COMPARATIVE STUDY OF CLONIDINE AND DEXMEDETOMIDINE AS ADJUNCTS TO ROPIVACAINE IN CAUDAL ANALGESIA IN CHILDREN

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DOCTOR OF MEDICINE

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CHENNAI

TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"COMPARATIVE STUDY OF CLONIDINE AND DEXMEDETOMIDINE AS ADJUNCTS TO ROPIVACAINE IN CAUDAL ANALGESIA IN CHILDREN"** is a bonafide record work done by **Dr.KASIRAJAN.G** under my direct supervision and guidance, submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for MD, Branch X –Anaesthesiology.

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DECLARATION

I Dr.KASIRAJAN.G declare that the dissertation titled **"COMPARATIVE STUDY OF CLONIDINE AND DEXMEDETOMIDINE AS ADJUNCTS TO ROPIVACAINE IN CAUDAL ANALGESIA IN CHILDREN"** has been done by me. This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D. Degree, Branch X–Anaesthesiology degree Examination to be held in April 2013. I also declare that this dissertation, in part or full was not submitted by me or any other to any other University or Board, either in India or abroad for any award, degree or diploma.

Place: Madurai

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CONTENTS

1. INTRODUCTION

Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Pain is an unpleasant subjective sensation which can only be experienced and not expressed, especially in children who would seem to conceal their feelings when suffering from pain. The primary reason to treat or prevent pain is humanitarian and this becomes even more important in children who rely completely on their parents or care givers for their well being.

Acute pain is associated with a brief episode of tissue damage or inflammation such as that caused by trauma or surgery. In most of the cases the intensity of the pain diminishes steadily over a period of time. The various methods of pain relief have their own disadvantages which prohibit their use in children for eg: narcotics in children because of their respiratory depression and other analgesics which cannot be given for sometime after general anaesthesia due to the fear of vomiting and aspiration, the objection to the needles in the case of parenterally administered analgesics.

The regional anaesthetic techniques significantly decreases post operative pain and systemic analgesic requirements. Caudal route was chosen for this study as it is one of the simplest and safest techniques in paediatric surgery with a high success rate. Epidural space in children favours rapid longitudinal spread of drugs and makes it effective in treating postoperative pain.

In this study caudal block was done after the induction of general anaesthesia and was used as an adjunct to intraoperative anesthesia as well as postoperative analgesia in children undergoing surgical procedures below the level of the umbilicus. Caudal analgesia reduces the amount of inhaled and intravenous anaesthetic drug requirement attenuates the stress response to surgery, facilitates a rapid, smooth recovery and provides good postoperative analgesia. In order to decrease intra operative and postoperative analgesic requirements and to prolong duration of analgesia after single shot caudal epidural blockade, various additives such as morphine, fentanyl, clonidine and ketamine with local anaesthetics have been studied.

Ropivacaine is a new long acting amino amide local anaesthetic agent. It is structurally related to bupivacaine and has been used for pediatric caudal analgesia. It provides pain relief with less motor blockade. Literature suggests that ropivacaine is less cardiotoxic than bupivacaine, hence ropivacaine may be a more suitable agent for caudal epidural analgesia especially in day care surgery.

Dexmedetomidine is a α_2 adrenergic receptor agonist. It has increased affinity to α_2 adrenergic receptors than clonidine and less α_1 adrenergic receptor actions. The main advantage of the dexmedetomidine is it higher selectivity were compared in Clonidine for α_{2A} receptor is responsible for analgesic, hypnotic and anxiolytic actions.

The objective of this study was to compare of the analgesic action of clonidine and dexmedetomidine combined with ropivacaine in caudal analgesia for children undergoing infra umblical surgical procedures.

2. HISTORY

1901 – SICARD and CATHELIN described epidural injection through sacral hiatus

1933 – CAMBEL M.F first described sacral epidural block in children and infants

1957 – Synthesis of Ropivacaine.

1960 - Clonidine hydrochloride was introduced.

1965 - Melzock and Walts propounded the Gate Control Theory of pain.

1974 - KAY B used caudal block for post operative pain relief in children.

1992 - Ropivacaine was introduced in clinical practice.

1999 - Dexmedetomidine was introduced in clinical practice.

3. AIM OF THE STUDY

1. To assess and compare the efficacy of dexmedetomidine and clonidine used as adjuncts to ropivacaine in caudal analgesia for children.

2. Duration of postoperative analgesia and the complications were also studied.

4. ANATOMY RELATED TO CAUDAL BLOCK

Anatomy of sacrum

Sacrum is a large wedge shaped bone. It is formed by fusion of the five sacral vertebrae. It articulates above with 5th lumbar vertebra and below with the coccyx .It has an anteriorly concave and posteriorly convex surface. The anterior surface bears four transverse lines which terminate on each side in four anterior sacral foramina. The anterior primary rami of the first four sacral nerves emerge from the anterior sacral foramina. The posterior surface is convex and in midline runs a bony ridge, the median sacral crest with 3 or4 rudimentary spinous processes. The lamina of the 5th and sometimes the 4th sacral vertebra fuse fail to fuse in the midline and thus the deficiency, formed is known as "**sacral hiatus**". The lateral margins of this space each bear a prominence called "**sacral cornu**" which represents the inferior articular process of the 5th sacral vertebra. (Figure1)

Sacral canal

It is a prismatic cavity running throughout the length of the bone and following its curves. Superiorly, it is triangular in its section and is

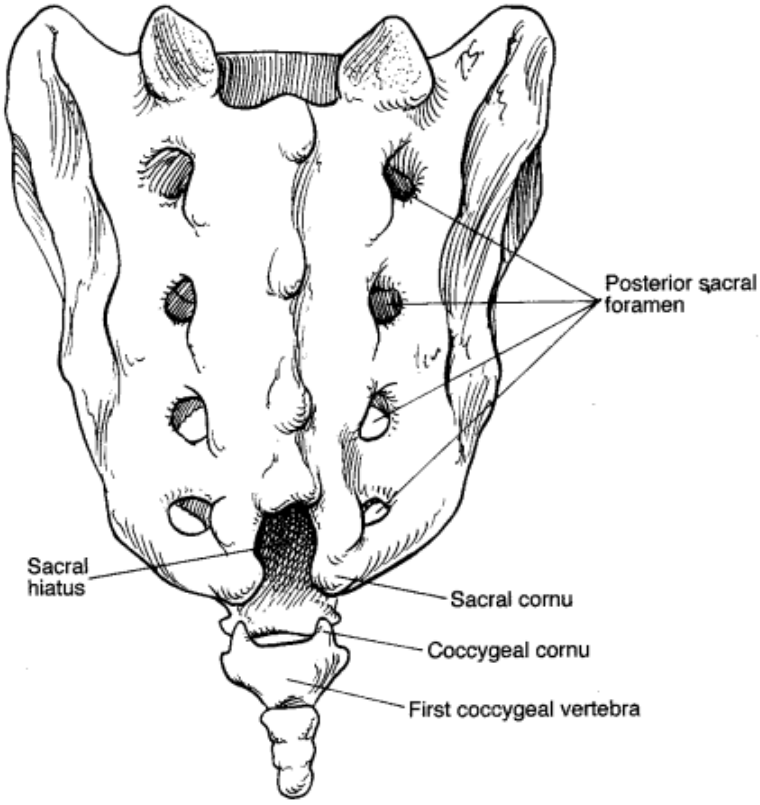


Figure 1: Anatomy of sacrum and hiatus

continuous with the lumbar epidural space. Its lower limit is the sacral hiatus closed by posterior sacrococcygeal membrane. Fibrous bands may be present in the canal and divide the epidural space into loculi which prevent the spread of solution and these may account for occasional incomplete anaesthesia.

Contents of the sacral canal

Sacral and coccygeal nerve roots with their dorsal root ganglia.

The filum terminale which is the continuation of piameter.

Epidural plexus of veins formed by the lower end of vertebral veins.

These vessels are numerous in the anterior aspect than the posteriorly.

Loose areolar and fatty tissue, which is more dense in males than in females.

Sacral hiatus

This is a triangular opening present in the posterior wall of the sacrum resulting from lack of fusion of the laminae of 5^{th} and may 4^{th} sacral vertebral arches. Its apex is at the level of the spine of 4^{th} sacral vertebra. In some cases the apex is at the level of 3^{rd} sacral spine due to the absence of the 3^{rd} and 4^{th} laminae and occasionally the whole of the bony posterior wall is deficient. When the laminae of the 5^{th} sacral vertebra are present, the hiatus may be very small with a diameter as narrow as 2mm. The hiatus is covered by the sacrococcygeal membrane and pierced by the coccygeal nerves and the 5^{th} sacral nerve. This membrane may be ossified in elderly subjects making the introduction of caudal needle difficult.

When local anaesthetic is injected into the sacral canal, it ascends upwards in the sacral epidural space for a distance proportional to the volume of the solution, force of injection, amount of leakage through the eight sacral foramina and the connective tissue in the space.

CAUDAL ANAESTHESIA

Selection of equipment:

Reliability of the technique and the incidence of complications largely depend on the characteristics of the needle used. The four important characteristics of the needle are – bevel, internal &external diameter, length, presence of the stylet.

Sharp bevelled needle:

Advantage – traverse easily through the tissues

Disadvantage

- Characteristic "give way" while puncturing sacrococcygeal membrane may not be clearly felt with sharp needles.
- Sharp needles have long bevel which may have to be advanced further into the epidural space so that it lies entirely within it.
- Cartilaginous sacrum can be easily traversed by a sharp and long bevelled needle that may lead to rectal puncture or iliac vessel puncture.
- Straight tipped needle with a bevel of 45-60 degree is ideal for caudal epidural anaesthesia.

Diameter:

Small needles may bend & break during procedure 21G, 22G, 23G are ideal because it is rigid and large enough to allow reflux of blood or CSF.

Length:

Proximity of dural sac makes it dangerous to use very long needles. The distance between skin and epidural space is almost always less than 20mm even in adults. So it is not advisable to use a needle longer than 30mm.Needle with stylet if used prevents formation of an epidermoid tumour due to skin tag. Epidural needle with 20G, 21G and 22G are employed when one intends to use an epidural catheter via caudal route to achieve anaesthesia at higher level after radiographic confirmation.

Determination of the volume of local anaesthetics:

Height of block – depends on the volume injected

Formula based on weight/ age:

Armitage formula

High sacral – 0.5 ml/kg

High lumbar – 1ml/kg

Thoracic level – 1.25ml/kg

Sclhute-Steinberg formula (8-12 years)

0.1ml /segment/ year <7years.

Weight is the best predictor. To calculate the total volume to be injected. Volume required in ml = 0.65 X number of segments to be blocked x body weight (kg)

Spiegal formula:

Total volume of injection (ml)= 4+(D-15)/2,Where D is the distance between from the spinous process of 7^{th} cervical vertebra to the sacral hiatus in cm.

Modified Spiegal formula:

Volume of injection (ml) = 4+(D-13)/2

Despite larger volumes of local anaesthetics used in children as compared to adults, peak plasma levels of the local anaesthetics in children remain far below the toxic levels than in adults. As the child grows space become less compliant and hence large volume can cause high spread of solution and an increase in the CSF concentration.

Maximum volume recommended for injection is 20ml.

Patient position:

Three positions can be used for caudal anesthesia;

1. Prone position - Most often chosen in adults.
2. Lateral decubitus position – This is the most commonly used position in paediatric age group. The lateral decubitus position is used in children because it is easier to maintain a patent airway in this position than in the

prone position and the landmarks are more easily palpable than in adults.

3. Knee-chest position – This is infrequently used.

Anatomical landmarks:

Classically hiatus is described as the apex of the triangle formed by joining the two posterior superior iliac spine and tip of the coccyx. (fig 2&3).

The point of puncture is at the midpoint of this triangular space. Intergluteal fold is not an ideal landmark because it will not always correspond to the midline. Left forefinger is placed in coccyx tip,the hiatus corresponds to the second crease of the finger palpation of this membrane gives a characteristic feel of a membrane under tension similar to that of a fontanelle.

TECHNIQUE

Area was prepared with antiseptic solution. Sterile drapes are placed around the site. The skin is punctured with the needle perpendicular and the bevel parallel to the sacrococcygeal membrane's long fibres Once needle crosses the sacrococcygeal membrane, a "give way" is felt after which make an angle between 20 to 30 degree to the skin. This is done to prevent the needle hitching against the anterior aspect of sacrum .The needle is advanced 2-3mm. so as to ensure that the entire needle bevel within the sacral canal.

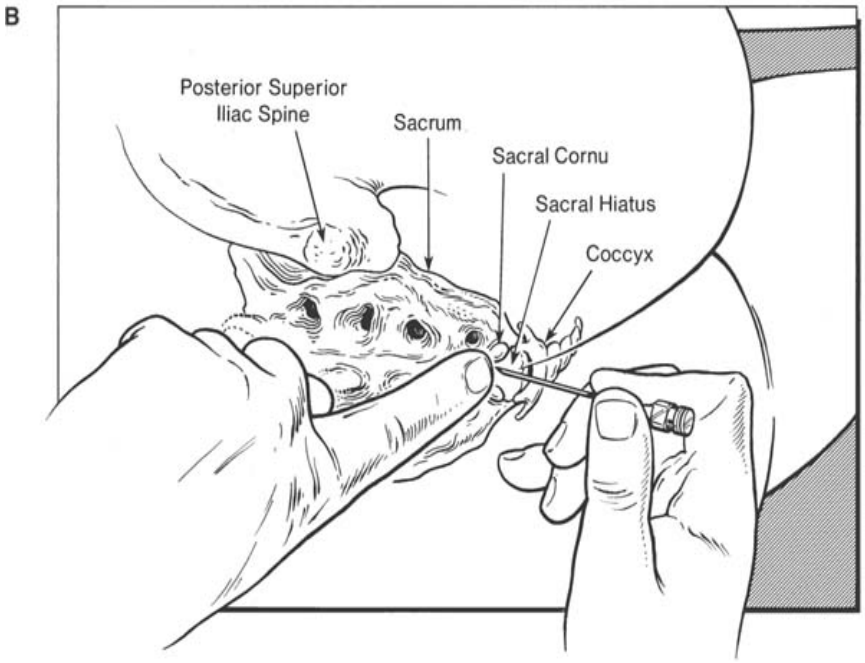


Figure 2 caudal technique.

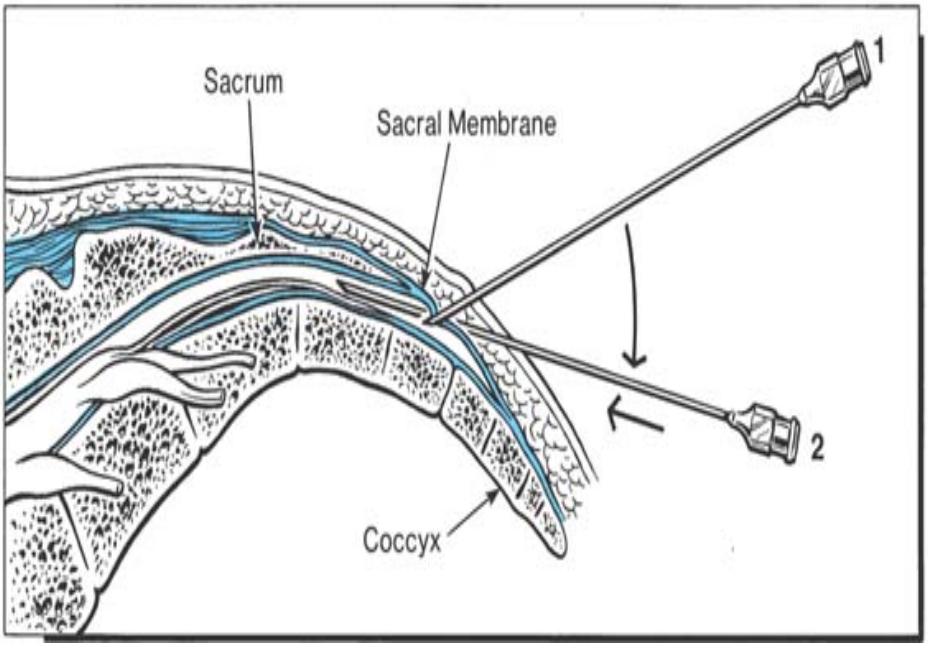


Figure 3: caudal technique.

CONFIRMATION OF SPACE

Whoosh test:

It is done by injecting air via the needle and another person should auscultate just proximal to the injection site. If the needle is correctly positioned in the caudal space, then the characteristic whoosh sound is heard when air is pushed.

Swoosh test

If the needle is correctly positioned in the caudal space, while injecting local anaesthetics, Swoosh sound is heard at a site just proximal to the hiatus.

It is suggested to avoid injection of air in children as it may cause patchy block and in a rare complication of pneumocephalus ,venous air embolism may also occur.

Other techniques commonly used to identify the space are:

- Easy injection of drug
- No resistance to injection
- No subcutaneous bulge

INJECTION OF DRUG:

After gentle asipration the drug is injected over a period of 60-90seconds. Irrespective of the speed injected (0.023-0.33ml/sec) syringe should be repeatedly aspirated during the course of injection. The patient is monitored for any change in Mean arterial pressure /heart rate. Faster injection causes increased cephalad spread resulting in higher block and respiratory problems.

Transient increase in intracranial pressure with transient loss of consciousness and headache can occur .On the other hand, too slow an injection increases the chance of lateralisation of the block or a lower level of anaesthesia as the drug tends to leak through the foramina and increases the risk of needle displacement.

INDICATIONS:

Ideal for lower abdominal and lower limb surgeries

Emergency: testicular torsion, strangulated hernia repair, paraphimosis, wound debridement of pelvis/ lower limbs.

Elective:

Repair of inguinal hernia, umbilical hernia, hydrocele, Orchidopexy, anorectal, genitourinary surgeries, pelvic, hip, phimosis and lowerlimb surgeries.

CONTRAINDICATIONS:

a) Hydrocephalus.
b) Seizure disorders.
c) Vertebral osteosynthesis.
d) Local skin infection.
e) Pilonidal sinus near hiatus.
f) Major sacral malformation –meningomyelocele.
g) Meningitis.

COMPLICATIONS

Possibilites due to error in the technique:

1. Subcutaneous injection.
2. Vascular puncture: 10-15%. Since epidural veins are valveless, injection may be immediately followed by convulsions, arrhythmias, hypotension and respiratory depression.
3. Dural puncture: If dura is punctured, withdraw the needle immediately. Second attempt can be made provided the drug is injected slowly under low pressure.
4. Subarachnoid injection may lead to total spinal even along cranial nerve distribution.
5. Bone marrow, rectal and intraosseous injection
6. Complete or partial failure of the block More common in > 7 years old.
7. Lateralization: occurs in 1 in 1000 cases When caudal is performed in lateral decubitus, 50% have a level of anaesthesia 2 dermatomes higher on the dependent side Slow injection may cause a difference of more than 4 dermatomes ; may be due to presence of a complete plica mediana dorsalis.
8. Un anaesthetised dermatomes.
9. Large size dermatomes like L5- S1 missed.

10. Neurological complications Urinary retention – most common if narcotics are used in caudal. Time to micturate may be delayed but not troublesome
11. Nerve injury is rare.
12. Other complications Vomiting, epidural infection , meningitis, shivering.

5. PHYSIOLOGICAL CONSIDERATION

Classification of sensory fibers

Sensory fibres	Speed of transmission	Sensory function	Myelination
C fibres	0.5 -2m/sec	Pain,cold, heat, touch.	Unmyelinated
A-Alpha fibres	70 -120m/sec	Noxious chemical thermal, mechanical stimuli	Myelinated
A-Beta fibres	30 -70m/sec	Light touch, pressures,vibration proprioception	Myelinated
A-Gamma fibres	30-70m/sec	Proprioception, Motor to muscle spindle	Myelinated
A-Delta fibres	12 -30 m/sec	Pain, cold, touch	Myelinated
B fibres	3 -15 m/sec	Pre ganglionic autonomic (sympathetic)	Myelinated

PAIN PATHWAYS

Pain receptors consist of peripheral plexus of unmyelinated nerves, activated by high-intensity stimuli which may be thermal, mechanical, electrical or chemical. Pain is conducted along two types of fibres in the periphery, A delta fibres are finely myelinated and relatively rapidly conducting (12-30 m/sec). They conduct the sharp pain produced by pin prick or electrical stimulation as well as thermal stimuli and responsible for withdrawal reflex.

A delta conducted pain is felt quickly and is well localised. 'C' fibres are very fine non-myelinated fibres which conduct at a very slow rate 2-3m/sec or less. Their threshold for stimulation is higher and is responsible for delayed and truly noxious burning or throbbing pain.

The activation of two different type of fibres (A delta &C) by noxious stimuli explains the double sensation for pain evoked in the human by a single short noxious stimulus, rapid pricking pain(0.1sec, latency, fast pain) carried by A delta fibres is followed approximately one second later by a burning pain (slow pain) mediated by C fibres.

Peripheral sensory nerves have their cell bodies in the dorsal root ganglion and the central projection of A delta and C fibre neurons enter the dorsal horn in the lateral division of the dorsal root.

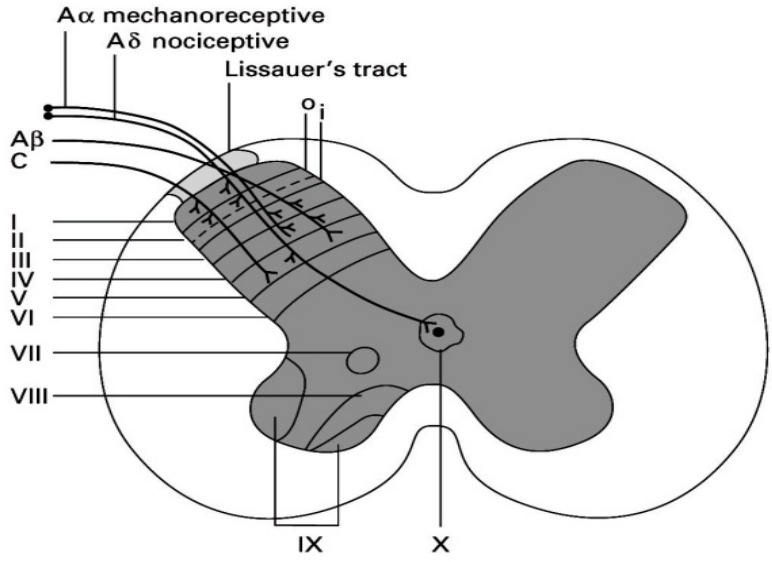


Figure 4 :Spinalcord laminae

In the grey matter of the spinal cord cell bodies are arranged in a series of laminae, some of which have classical names but which are more simply given roman numerals by Rexed, starting with I at the tip of the dorsal horn. A delta and C primary afferent fibres terminate principally in the marginal layer (lamina I) and the substantia gelatinosa (lamina II) of the spinal cord (fig.4). Some of the neurons of the lamina I which synapse with A delta fibres, give off axons which ascend in the contralateral anterior columns without synapsing with neurons from deeper layers. The majority of the pain fibres, however synapse in the substantia gelatinosa into intermediate neurons which sent projections to deeper layers or with the dendrites of neurons whose cell bodies reside in deeper layers, principally in lamina V.

The central projection from cell bodies in lamina IV, V & VI with contribution from lamina I, cross midline in the anterior commissure to form the spinothalamic tract, which ends in thalamus, principally in the ventroposterior nucleus, sending a few fibres enroute to the periaqueductal grey matter. The ventroposterior nucleus of the thalamus projects to the post central gyrus, the sensory cortex.

Pain stimuli can also pass via interneurons to cell bodies in the intermediate grey matter (laminae VII & VIII) whose central projections also ascend in the contralateral anterolateral columns, forming

Spinothalamic Pathway

While it appears that the thalamus is involved in the experience of pain, the post-central gyrus is necessary for its accurate localization and prefrontal cortex for unpleasant affective reactions to it.

INHIBITORY PATHWAYS:

1. Large primary afferent fibres, which mainly ascend in the dorsal columns and whose cell bodies lie in the dorsal root ganglion send collaterals to synapse with and activate inhibitory inter neurons in the dorsal horn. These inturn inhibit release of transmitters along pain pathways. Thus, stimulation of large A beta cutaneous afferents may inhibit pain transmission (gate theory of Melzack and Wall).
2. Inhibitory fibres, which descend in the dorsolateral white funiculus and whose cell bodies lie in the medullary raphe nuclei, may also inhibit pain transmission presumably by an action of the inhibitory interneurons. Activity in these descending inhibitory fibres may be provoked by stimulation of the cell bodies in the medulla directly or of the periaqueductal grey matter.

PHYSIOLOGICAL CHANGES

While activity in sensory neurons may be excited in the periphery by thermoreceptor, nociceptor or mechanoreceptor stimulation cell bodies in the posterior horn are responsive to different intensities of stimulation. Thus certain cells found principally in lamina IV respond only to a low intensity of stimulation such as light touch. These are termed low threshold or LT cells. They respond maximally to low- threshold stimuli and do not increase their firing rate with increased stimulus intensity. They are therefore incapable of conducting pain. Another type of cell, found principally in lamina V responds over a wide range stimulus intensities, the so called wide-dynamic range or WDR cells. Noxious stimuli can excite a variable response in WDR cells in lamina V, a third type of cell is responsive to stimuli only within the noxious range. Such cells are known as High threshold cells or HT cells and are found mainly in lamina I. A delta and C fibre stimulation in the periphery results in increased firing in HT and WDR cells in lamina I and V which is conducted up in spinothalamic tract. (Fig 5) Surgery produces local tissue damage with consequent release of algesic substances like prostaglandins, histamine, serotonin, bradykinin, hydroxytryptamine, substance P and generation of noxious stimuli that are transduced by nociceptors and transmitted by A delta and C fibres to the neuraxis.

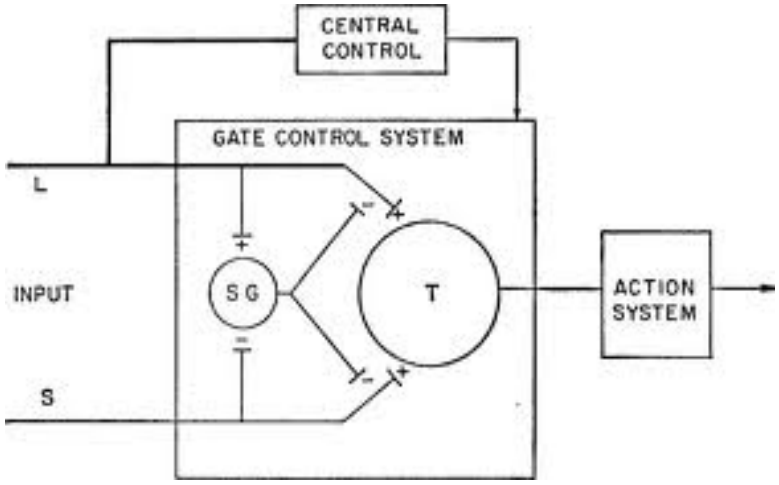


Figure 5: Gate control theory.

L.glutamate is the only excitatory aminoacid which is concentrated in the dorsal horn. There are a number of receptors for glutamate namely NMDA (N methly D aspartate), AMPA (α amino3 hydroxy 5 methyl- isoxazole 4 propionate), L-2 amino-4-phospono butyrate(LAP4), kainite and metabotropic receptors. The majority of the opioid receptors in the dorsal horn are mu receptors although delta and kappa receptors are present.

Segmental reflex responses associated with surgery includes increased skeletal muscle tone and spasm with associated increase in O2 consumption and lacticacid production. Stimulation of sympathetic neuron causes tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption. Suprasegmental reflex responses result in further increase in sympathetic tone and hypothalamic stimulation, metabolism and increased O2 consumption. Hence the most obvious motive for relieving postoperative pain is not only humanitarian but also to contribute a more rapid and complete postoperative recovery.

6. APPLIED PHARMACOLOGY

A. PHARMACOLOGY OF ROPIVACAINE

Ropivacaine is the new amino amide local anaesthetic. It is a derivative of pipecoloxylidide. Pipecoloxylidide was first synthesized in 1957. Pipecoloxylidide are chiral drugs due to asymmetric carbon atoms and form two groups of S and R enantiomers. Ropivacaine is a pure S enantiomer with chiral purity of 99.5%. Ropivacaine is prepared by alkylation of S enantiomer of dibenzoy-l-tartaric acid

PHYSIOCHEMICAL PROPERTIES:

Chemical name as S-1-propyl-2,6- pipecoloxylidide hydrochloride monohydrate. (Figure 6)

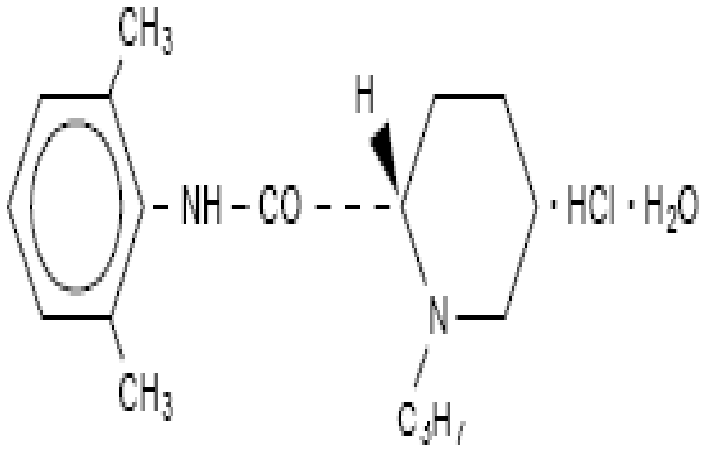


Figure6: Chemical structure of Ropivacaine

Molecular weight	-	274
Pka	-	8.07
pH	-	7.4
Protein binding	-	94%
Partition coefficient (lipid solubility)	-	8.7
Mean uptake ratio	-	94
T1/2	-	111 minutes,
Clearance	-	10.3 L/minutes.
Solubility in H2O at 25^0C	-	53.8g/L
Specific gravity	-	1.002 to 1.005 at 25^oC.

MECHANISM OF ACTION:

Ropivacaine acts through inhibition of sodium channel. It inhibits the conduction of sodium ions through the channel and also potassium channel. Thus it blocks the generation and conduction of impulses across the nerve fibres. This type of block is reversible.

PHARMACOKINETIC PROPERTIES:

Absorption

The plasma concentration of ropivacaine is dependent on many factors like route of administration, dose of drug administered, concentration of drug used, vascularity of the region and hemodynamic status of patient. It shows the biphasic absorption phase from the epidural space. The mean half life is 14 minutes in first phase and 4 hours in second phase. The rate limiting factor is

the slow absorption from the epidural phase. Thus it has longer duration of action through the epidural route.

Distribution

The steady state plasma concentration after intravascular injection is about 59+7 liters in total volume of distribution. The protein bound fraction is about 94%. It mainly binds to α–1- acid glycoprotein. There is an increase in bound form of drug in post operative state due to increase in α-1-acid glycoprotein from stress response in surgery. This is especially so after continuous epidural infusion. Ropivacaine can easily cross the placenta and equilibrium is reached.

Metabolism

Ropivacaine is extensively metabolized in the liver. It is predominantly metabolised by aromatic hydroxylation involving cytochrome P4501A to 3-hydroxy ropivacaine. About 37% of the total dose is excreted in urine. It is excreted in both free and conjugated form of 3-hydroxy ropivacaine. There is a low concentration of 3-hydroxy ropivacaine in the plasma. Another metabolite, 2-hydroxymethyl - ropivacaine has been identified but is not quantified in the urine. 3-OH-ropivacaine and N-de-alkylated metabolite of ropivacaine are the major metabolites excreted in the urine. These are especially formed during the continous epidural infusion. There is no reacemerization between the S and R forms in the body.

Elimination

Ropivacaine is mainly eliminated through the kidney as various metabolites.About 86% of the total drug is excreted through the kidneys. The total clearance is about 387 ml/min. The mean half life is about 1.8 hours after intravascular injection and about 4.2 hours after epidural injection.

PHARMACODYNAMIC PROPERTIES:

Action on Nervous system

The type of blockade produced by ropivacaine depends upon the concentration of drug used. In low concentration it blocks both Aδ and C fibres which is more potent than that of equal concentration of bupivacaine. In high concentration, the blockade of Aδ fibres' is less than that of bupivacaine while the blockade of C fibres is similar. The penetration of ropivacaine into myelin sheath is less due to low lipid solubility compared to bupivacaine. Thus it preferentially blocks C fibres than Aδ fibres. This causes less potent motor blockade.

The addition of epinephrine does not influence the type of blockade produced. In toxic doses, it causes initial excitation of nervous system manifesting as restlessness, tremor, and convulsions. Later it leads to depression of medullary centre and coma.

Effect on Cardiovascular system

The effects are mostly due to blockade of sympathetic fibers. There is decreased venous return and decreased heart rate which produces hypotension.

Effect on respiratory system

Ropivacaine does not have any marked effect on the respiratory system in normal doses. Higher doses leading to toxicity of drug produces respiratory depression secondary to medullary depressant effect.

INDICATIONS

Surgical anaesthesia:

a) Spinal anaesthesia.

Epidural anaesthesia.

Caudal anaesthesia.

Peripheral nerve block and infiltration anaesthesia.

Pain management:

a) Labour analgesia – intermittent bolus or continous infusion

    a. more in walking epidurals

Post operative pain management – epidural infusion as

    i. Intermittent bolus.

    ii. Continous infusion.

    iii. Patient controlled analagesia.

Pain management in paediatrics:

a) Caudal epidural block.

b) Peripheral nerve block for intra and postoperative pain management.

CONTRAINDICATIONS

a) Known cases of allergic reactions to amide type of local anaesthetics.

b) Intravenous regional anaesthesia (Bier's block).

c) Obstetric Para cervical anaesthesia.

d) Hemodynamic instability.

e) Septicemia.

f) Local site infection.

ADVERSE EFFECTS

The adverse reactions to ropivacaine are related to excessive plasma levels due to excess dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses of plasma level when toxicity begin to occur are about 4.3 and 0.6 μg/ ml of total and free plasma concentrations respectively. The toxic levels are reached in cases of continuous epidural infusion as the drug is administered for long times.

THE VARIOUS POSSIBLE SIDE EFFECTS :

g) Cardiovascular System – bradycardia, hypotension, vasovagal reaction, syncope, arrhythmias. Due to low lipid solubility the cardiotoxic potential is less than that seen with bupivacaine.

h) Central and peripheral nervous System – dyskinesia, hypokinesia, neuropathy, vertigo, tremors, paresis, neropathy and coma.

i) Gastrointestinal System - nausea and vomiting, incontinence, tenesmus.

j) Hearing and Vestibular - tinnitus, hearing abnormalities.

k) Hepato - Biliary System – jaundice

l) Musculoskeletal System – myalgia.

m) Psychiatric Disorders - agitation, confusion, nervousness, amnesia, hallucination, emotional liability, insomnia, nightmares.

n) Skin Disorders - rash, urticaria.

o) Urinary System Disorders- urinary incontinence, micturition disorder.

p) Vascular - deep vein thrombosis, phlebitis, pulmonary embolism.

AVAILABILITY

Ropivacaine is available in ampoules of isobaric solution in concentration of 0.2%, 0.5%, 0.75% and 1%. The solutions are prepared in preservative free form.

DOSAGES

a) Caudal - 1ml/kg of 0.2% solution.

b) Epidural - 15 to 20 ml of 0.2% or 0.5% solution.

c) Spinal - 3 to 4ml of 0.5% or 0.75% in adults. 0.3 to 0.5mg/kg of 0.5% solution in children.

d) Peripheral nerve block – 15 to 30 ml of 0.15% to 0.5%. The toxic level is reached when more than 2mg/kg of drug volume is used.

B. PHYSIOLOGY OF α2-ADRENOCEPTORS

α_2 - receptors are found in many sites throughout the body. α_2 adrenoceptors are found in peripheral and central nervous systems. It is also present in effector organs such as the liver, kidney, pancreas, eye vascular smooth muscles and platelets. Physiologic responses mediated by α_2 adreno-ceptors vary with location and can account for the diversity of their effects.

The classification of α_2 - receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations. α_2 - adrenoceptors are divided into three subtypes; each subtype is responsible uniquely for some of the actions of α_2 - receptors. (Fig 7)

α_{2A} is the predominant subtype in CNS and responsible for the sedative, analgesic and sympatholytic effect.

α_{2B} is found mainly in the peripheral vasculature and responsible for the short-term hypertensive response.

α_{2C} is found in the CNS and responsible for the anxiolytic effect. All the subtypes produce cellular action by signaling through a G-protein which couples to effector mechanisms. This coupling appears to differ depending on the receptor subtype and location. The α_{2A}-adreno-ceptor subtype seems to couple in an inhibitory fashion to the calcium channel in the locus ceruleus of the brainstem, whereas in the vasculature the α_{2B}-adrenoceptor sub type couple in an excitatory manner to the same effector mechanism.

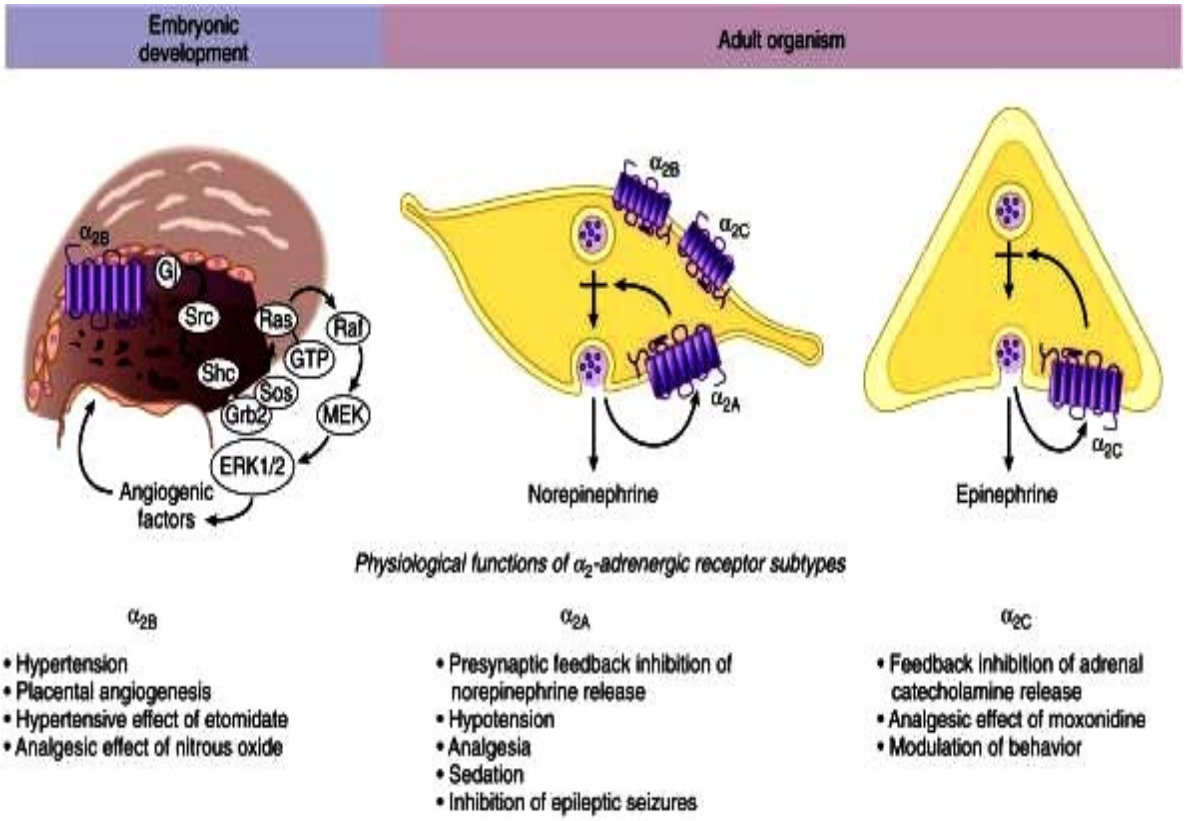


Figure 7: Alpha 2adrenergic receptors

C. PHARMACOLOGY OF CLONIDINE HYDROCHLORIDE

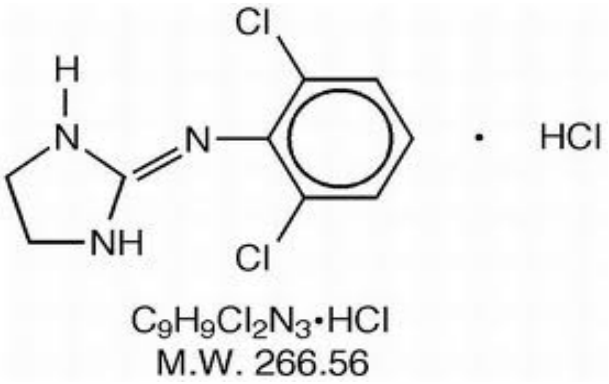


Figure 8. Chemical structure of clonidine hydrochloride.

Introduction:

Clonidine hydrochloride is a centrally acting selective partial alpha 2 agonist introduced in early 1960s.It was initially used as a nasal decongestant .Its anti hypertensive property was found out after that. Subsequently more insight into the pharmacological properties has led to its use in clinical anaesthesia practice as well.(Fig 8) It is an imidazoline compound and exists as a mesomeric compound. The chemical name is 2-(2,6- dichlorophenylamino)-2 imidazoline hydrochloride. The structural formula is C9H9CL2N3HCL. The molecular weight is 266.56. Clonidine is an odourless, bitter, white, crystalline substance soluble in alcohol and water. Clonidine improves the quality of anaesthesia provides a more stable cardiovascular course during anaesthesia presumably because of their sympatholytic effect and need for lower dose of cardio active anaesthetic and reduces the dose requirement of the anaesthetic agent. Clonidine reduces the halothane MAC by up to 50% in a dose dependent

manner. Clonidine potentiates the anaesthetic action of the local anaesthetics with fewer side effects in peripheral nerve blocks and central neuraxial blockade.

Availbility:

Available as one ml ampoule containing 150 micrograms. It should be stored below 25 degree Celsius. It also available as tablet.

Mechanism of action:

Clonidine is a centrally acting partial α2 adrenergic agonist with a selectivity ratio of 220: 1 in favour of α2 receptors.When clonidine was injected into epidural space it is penerates the blood brain barrier and reaches to the hypothalamus and medulla. It is stimulates the inhibitory α2 adrenergic receptors to reduce the central neural transmission in the spinal neurons.

The α2 adrenoreceptors are densely found in the locus ceruleus, whch is an important source of sympathetic nervous system innervation of the forebrain .Clonidine is an inhibitor of pontine locus ceruleus as it stimulates the α2 adrenergic neurons in the medullary vasomotor centre, which reduces the sympathetic nervous system outflow from central nervous system to peripheral tissues. The sympathetic nervous system outflow reduction is caused by peripheral vaodilatations and leads to decrease the blood pressure, heart rate and cardiac output.

Clonidine reduces the anaesthetic requiremet and its analgesic effects due to modification the potassium channels in the central nervous system and hyperpolarisation in the cell membranes.

Clonidine is neuraxial inhibits of spinal substance-P release is believed to be involved in the analgesic effect. Another contribution to analgesic effect may be through the release of acetylcholine in the neuraxial region. The α2 adrenergic agonist also enhances analgesia from intraspinal opioids. Sedation is produced by its action on locus ceruleus.

The α2 adrenoreceptors terminals are presented centrally, peripheraly, superficial laminae of the spinal cord and brain stem neuclei is believed to involved analgesic effects after neuraxial administration of clonidine.it also reduce the cold response threshold and increase the sweating threshold may inhibition of the shivering response.

Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of the opposing action at multiple sites. In the nucleus tractus solitories and locus ceruleus of the brain stem, activation of post-synaptic α2 adrenoreceptors decrease the sympathetic actions. producing hypotension and anti- arrythmogenic action.

In peripheral nerves it produces a minor degree of blockade at high concentrations with some preference for C- fibres and this effect in part enhance the peripheral nerve block when added to local anaesthetics, probably because the α2 adrennoreceptors are lacking on the axons of peripheral nerves.

Pharmacokinetics:

Clonidine well absorped from orally and bioavailability of clonidine is 75 to 95%. It is peak plasma half life is 60 to 90 minutes, Plasma half life is 12 to 33 hours.50% of the drug is mainly metabolized in the liver whereas it is excreted in an unchanged form by the kidney 40 to 60%, and its half life can increase in the presence of renal dysfunctions. A transdermal delivery system is available in which the drug is released at a consant rate for a week. Three or four days are required to achieve steady state concentration.

After 300µgm/ kg intravenously infused over 10 min produces:

Distribution t½: 11± 9 minutes

Elimination t½: 9± 2 hours, 41 hours in severe renal dysfunction.

Volume of distribution: 2.1± 0.4 l / kg

Plasma protein binding: 20 - 40% in vitro.

DOSAGE REGIMEN:

Oral: 3-5µg/kg.

Intramuscular: 2 µg/ kg.

Intravenous: 1-3µg/kg.

Spinal: 50 -100µg.

Caudal: 1-2µg/kg.

Epidural: 1-2µg/kg.

Transdermal: 0.1-0.3 mg released per day.

PRECAUTIONS:

1. In renal insufficiency patients, lower dose is needed.
2. Sudden withdrawal of prolonged continuous epidural infusion roduces hypertensive crisis. So gradually discontinue over 2 to 4 days to prevent this complication.
3. Use with caution in patients with cerebrovascular or coronary insufficiency.
4. Patient on beta blocker therapy,beta blocking drugs should be withdrawn several days before the epidural clonidine.

CONTRAINDICATIONS:

1. Known hypersensitivity to clonidine or components of the product.
2. Brady arrhythmia or AV block.
3. Severe cardiovascular disease.
4. Cardiovascular / hemodynamic instability.

INTERACTIONS:

1. Clonidine may potentiate the CNS- depressive effect of alcohol, barbiturates or other sedative drugs.
2. Clonidine potentiate the hypotensive action with narcotic drugs.
3. The hypotensiveeffects of the clonidine is antagonized by tricyclic antidepressant.

4. Concomitant administration of drugs with a negative chronotropic or dromotropic effect (beta blocker, digoxin) can cause or potentiate bradycardia and rhythm disturbances.
5. Beta blockers may potentiate the hypertensive response seen with clonidine withdrawal.

USES:

1. Caudal anaesthesia: 1to2µg/kg of clonidine combined with local anaesthetic agents prolong the duration of analgesia by 2 or 3 times without hemodynamic side effects.
2. Epidural block: Clonidine as sole agent or in combine with opioids or local anaesthetics to provide excellent analgesia in labour analgesia.
3. Spinal anaesthesia: Clonidine combined with local anaesthetics improves the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.
4. Pre anasthetic medication : Oral clonidine is 5 micg/kg.

a. Blunts reflex tachycardia associated with direct laryngoscopy for intubation of trachea.
b. Reduce the intraoperative instability of the blood pressure and heart rate.
c. Plasma catecholamine concentrations levels decreased.
d. Dramatically decrease anaesthetic requirements of inhaled and injected drugs.

5. In Peripheral nerve blocks: Clonidine prolongs the duration of anaesthesia and analgesia with local anaesthetics by two times in a dose of 75 to 150 micro grams.
6. In Bier's Block: 150 microgram of clonidine enhances the tolerance of tourniquet.
7. It is also used in intra articular analgesia.
8. Protection against perioperative myocardial ischemia: Clonidine decreases myocardial ischemia, infarction and mortality following cardiovascular surgery.
9. In the management of hypertensive crisis clonidine is useful.
10. Treatment of shivering; Administration of clonidine75µg IV abolishes shivering by inhibiting thermoregulatory control.
11. Clonidine is useful in the treatment of opioid and alcohol withdrawl syndrome.

Side effects;

1. The most common side effects are sedation and xerostomia.
2. Cardiovascular complications are bradycardia, hypotension, and sinusnode arrest, junctional bradycardia, high degree AV block and other arrhythmia are reported rarely. Occasionally bradycardia may requires treatment with I.V anticholinergics.Orthostatic hypotension occurs rarely.
3. Rebound hypertension; Abrupt discontinuation of clonidine can result in rebound hypertension as soon as 8 hours and as late as 36 hours after the

last dose. Symptoms of the rebound hypertension are headache, abdominal pain, tachycardia, nervousness, and diaphoresis, which often precede the actual increase in systemic blood pressure. Labetalol is useful in the treatment of rebound hypertension.

4. Skin rashes occur frequently.
5. Impotence occurs occasionally.

Treatment for over dosage:

There is no specific antidote for clonidine over dosage. Measures like atropine, ephedrine, and i.v. fluids are enough in the management.Yohimbine partially reverses the analgesia and sedation but not the blood pressure and heart rate changes produced by the epidural clonidine.

D. PHARMACOLOGY OF DEXMEDETOMIDINE

Dexmedetomidine is an α_2 adrenergic agonist. The $\alpha_2$adrenergicreptors agonists produce sedation, anxiolysis, hypnosis, analgesia, and sympatholysis.It is a nonselective α_2 agonist with a 1600 greater selectivity for α_2 receptor as compared to α_1 receptor. Introduced in clinical practice 1999 and approved by FDA only for short-term, less than24 hours sedation and analgesia for ICU adult patients. Now a days used off-label outside of the ICU for sedation, adjunct analgesia, sedation for short term diagnostic procedures. It decreases the sympathetic tone and also attenuates the stress response during intubation and surgery. They are also used as adjuvants during intravenous regional anaesthesia.

Physicochemical Characters:-

It is a potent, highly selective α2 adrenergic agonist. Its freely water soluble. Molecular formula is C13H16N2.HCl.

Molecular weight: 236.74.

The chemical name as 4-(S)-[1-(2,3dimethylphenyl)ethyl]-1H-imidazole monohydrochloride.

It is a d-enantiomer of medetomidine. This substance has been used for sedation, hypnosis and analgesia in animal science for many years. It has high ratio of specificity for the α_2 receptor compared with clonidine.

Postsynaptic α_2 adrenoreceptors which are located in the peripheral blood vessels produce vasoconstriction. Presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine and leads to fall in blood pressure and heart rate.

The α_2 adrenoreceptors also located in central nervous system and spinal cord. It inhibits the neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. (Figure.9)

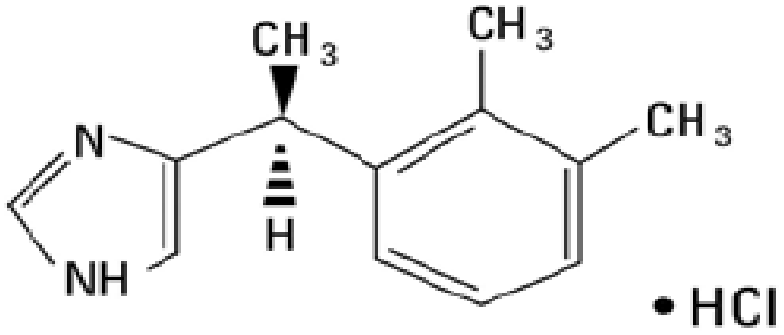


Figure:9. Chemical structure of dexmedetomidine hydrochloride.

MECHANISM OF ACTION

α_2 adrenoreceptors belongs to the large family of G protein coupled receptors, which contains a characteristic structure of seven transmembrane α helices.α2 adrenergic receptors activation are the decreased activity of adenylcyclase, which in turn inhibits the opening of voltage gated calcium channels and thus augments the hyperpolarizing potassium ion channel activity.

METABOLISM AND PHARMACOKINETICS

Dexmedetomidine is 94% protein bound.It undergoes an extensive hepatic metabolism. It is rapidly distributed and extensively metabolized in the liver by glucuronidation, conjugation, N-methylation, or hydroxylation and cytochrome P450 mediated metabolism. Metabolites are excreted in the urine (about 95%) and in the feces(4%). Dose needs to be adjusted in patients with liver impairment, but dose need not be adjusted in renal dysfunction patients. Large doses can produce the vasoconstriction leading to reduced drug volume of distribution.

Dexmedetomidine follows the nonlinear pharmacokinetics.

Elimination half life:- 2 to 3 hours.

Distribution half life: - 6 minutes.

Volume of distribution (vss):-118 litres.

Context-sensitive half-time: - Ranges from 4 minutes after a 10-minutes infusion to 250 minutes after an 8-hour infusion.

It has shorter duration of action compared to clonidine. The most frequently observed side effects in patients receiving dexmedetomidine include hypotension, hypertension, nausea, bradycardia and atrial fibrillation.

Dexmedetomidine cannot be used in patients with severe valvular heart diseases or ischaemic heart disease, elderly patients, Diabetes mellitus patients, Complete heart block as it decreases sympathetic nervous activity.

Dexmedetomidine does not affect the synthesis, storage or metabolism of neurotransmitters and does not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the specific α2antagonist, Atipamezole which acts by increasing the central turnover of norepinephrine. Its duration of action is 2 hours.

DOSAGE

It is available as100 mcg in1 ml ampoule or 2 ml vial. It is containing 100mcg/ml. It is generally diluted in 50ml of 0.9% normal saline to obtain concentration of 4mcg/ml.

DRUG INTERACTIONS

CYP2A6 inhibitors such as isoniazid, methoxsalen, miconazole, may increase the level and effects of dexmedetomidine. Conversly may increase the levels and effects of CYP2D6 substrates which include amphetamines, selective betablockers , lidocaine. Dexmedetomidine may decrease the levels and effects of CYP2D6 prodrug substrates, such as codeine, oxycodeine and tramadol. It has a weak inhibiting effect on cytochrome P 450 enzymes, so it may lead to increased plasma concentration of opioids when used concurrenly. Adverse reactions associated with dexmedetomidine such as hypotension, bradycardia may be augmented or potentiated by vasodilators and negative ionotropic drugs like digoxin and esmolol.

ADVANTAGES

- It is a Sedative and analgesic drug that produces sympatholysis without any respiratory depression.
- It is also an antisialogogue.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Sedation

It produces its effect by acting on the α_2 receptors present in the locus caeruleus and analgesic effect due to its action on α2 receptors within the locus caeruleus and spinal cord. It produces natural sleep with minimal respiratory depression. The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems like benzodiazepines.

Patients receiving dexmedetomidine infusions of sedation regimen in ICU setting have been described as being very easy to wake up and having the ability to follow commands but are able to recall the events in the ICU. It is easy to perform the daily wake up tests. In this critical test, mechanically ventilated ICU patients are taken off all sedatives to assess their mental status and titrate sedation.

The α_2 agonists act through the endogenous sleep-promoting pathways to exert their sedative effect.

Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus which in turn leads to

increase in GABAergic and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and sub cortical projections.

The α_2 agonists inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels.

Dexmedetomidine can produce profound sedation, and it has been used as a total IV anaesthetic when given at 10 times the normal sedation concentration range.

It produces cerebral protection by decreasing cerebral blood flow without affecting CMRO2, decreases cerebral blood flow velocity.

It has minimal effect on the cortical evoked potentials. It also ablates memory in a dose dependent manner.

The α_2 agonists have the advantage that their effects are readily reversible by α_2-adrenergic antagonists (e.g., atipamezole). It is administered in the dose of 50µg/kg I.V.

Atipamezole is not currently approved for human use. Similar to other adrenergic receptors, the α_2 agonists also show tolerance after prolonged administration.

Dexmedetomidine can also be used for addiction treatment, rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced benzodiazepine and opioid tolerance after prolonged sedation.

Analgesia:-

When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF. The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Onset of action via epidural route is 5 to 20 minutes. The primary site of analgesic action is thought to be at the spinal cord. It produces prolonged analgesia and increased duration of sensory and motor blockade when administered intrathecally along with bupivacaine.

RESPIRATORY EFFECTS:-

Dexmedetomidine throughout a broad range of plasma concentration has minimal effects on the respiratory system. Co administration of dexmedetomidine with other sedatives, hypnotics or opioids is likely to cause additive effects. It decreases the minute ventilation in a dose dependent manner. At lower concentrations, no effect on arterial oxygenation and pH. With increasing concentration, increased respiratory rate is observed.

CARDIOVASCULAR EFFECTS:-

No rebound hypertension is observed as compared to clonidine. It decreases the myocardial oxygen consumption; there is increased redistribution of blood from non ischaemic zone to ischaemic zone. It leads to increased flow in epicardial and endocardial vessels.

PERIOPERATIVE USES OF DEXMEDETOMIDINE

A. Premedication

Dexmedetomidine is anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties, which makes it suitable as a premedication agent. Dexmedetomidine decreases the thiopentone(30%) dose requirement, decreases the haemodynamic response to intubation, decreases volatile anaesthetic requirement .It should be administered at a dose of 0.3-0.6µg/kg intramuscular injection given 15minutes before surgery The administration of intramuscular dexmedetomidine at a dose of 1 µg/kg for premedication in outpatient cataract surgery resulted in sedation, and decrease in intraocular pressure without significant hypotension or bradycardia. Also the administration of dexmedetomidine for premedication decreases oxygen consumption intraoperatively by 8% and postoperatively by 17%.

Indications for the use of dexmedetomidine as premedication include patients susceptible to preoperative and peri operative stress, drug addicts and alcoholics, chronic opioid users and hypertensive patients.

B. Intra operative uses of dexmedetomidine

Intra operative uses of dexmedetomidine include its use as an adjunct to general anaesthesia, as an adjunct to regional anaesthesia, in monitored anaesthesia care (MAC) or as a sole agent for total intravenous anaesthesia (TIVA).

1. Used an adjunct to general anesthesia

The use intraoperative dexmedetomidine may increase hemodynamic stability because of attenuation of the stress-induced sympathoadrenal responses to intubation,decreased level of plasma catecholamines during surgery and during emergence from anesthesia.

Administration of intravenous dexmedetomidine decreases the narcotic consumption intraoperatively and post operatively when compared to propofol.

It reduces the vasoconstriction and the shivering threshold and is associated with a lower incidence of shivering.

It decreases the muscle rigidity caused by high doses of opioids. It also decreases the cardio stimulatory effects and post anaesthetic delirium produced by ketamine.

2. Used for regional anesthesia

The use of dexmedetomidine as adjuvant in regional anesthesia is approved.There is significant prolongation of sensory and motor block as compared to bupivacaine alone. Intrathecal α2-adrenergic agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics.The prolongation of the motor block of spinal anesthetics may result from the binding of α2-adrenergic agonists to motor neurons.

3. Used in monitored anesthesia care

Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, mild analgesia, lack of respiratory depression and hemodynamic stability at moderate doses. These properties allow dexmedetomidine to be an almost ideal agent for MAC despite its lack of amnesia and poor controllability because of its slow onset and offset.

Dexmedetomidine in MAC was used successfully in many situations: when patient arousability needed to be preserved, as for awake craniotomy , awake carotid endarterectomy and for vitreoretinal surgey. In addition, dexmedetomidine was used for sedation in difficult airway patients; during fiberoptic intubation, and for sedation of a patient with difficult airway undergoing lumbar laminectomy surgery in the prone chest position under spinal anesthesia.

4 .Use of dexmedetomidine as a sole anesthetic agent

Dexmedetomidine used as a sole anesthetic agent. Does not produce any respiratory depression, hypotension and severe bradycardia. These effects were maintained at higher doses without hemodynamic instability.It can be safely used in patients who are susceotible to narcotic induced respiratory depression.

C. Use of dexmedetomidine in postoperative period

Dexmedetomidine in addition to its sympatholytic effects, analgesic effects and decreased rate of shivering, the preservation of respiratory function allows the continuation of the dexmedetomidine infusion in the extubated,

spontaneously breathing patient. The possibility of ongoing sedation and sympathetic block could be beneficial in reducing high rates of early postoperative ischemic events in high-risk patients undergoing non-cardiac surgery.

Perioperative administration of dexmedetomidine could be beneficial in chronic opioid users and alcoholics, in high-risk patients as well as in cardiac patients with good to moderately decreased left ventricular function.

D. Use of Dexmedetomidine in the pediatric-age group

In pediatric-age group uses of intraoperative dexmedetomidine at different doses with the goal of reducing the post sevoflurane agitation in children aged 1-10 years. The optimal dose of dexmedetomidine was 0.3 μg/ kg and its use did not result in adverse effects. When compared with propofol for sedation during MRI, dexmedetomidine provides adequate sedation during the scan but has a slower recovery profile.

One of the major advantages of dexmedetomidine over other sedatives is its respiratory effects, which are minimal in adults and children. It does not lead to extreme hypoxia or hypercapnia. Indeed, respiratory rate, CO_2 tension, and oxygen saturation are generally maintained during dexmedetomidine sedation in children.

CONTRAINDICATIONS

A. Severe bradycardia and cardiac conduction abnormalities.

B. Ventricular dysfunctions - ejection fraction<30%.

C. Patients with hypovolemia or hypotension.

ADVERSE EFFECTS

1. Central and Peripheral nervous system: Dizziness, headache, neuralgia, neuritis, speech disorder, Convulsion
2. Gastrointestinal System :

   Abdominal pain, diarrhea, vomiting, nausea, dry mouth
3. Cardiovascular systems:

   Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, Twave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
4. Hepato Biliary System:

   Increased gamma glutamyl transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase.
5. Metabolic and Nutritional Disorder:

   Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, and hypoglycemia.

6. Psychiatric Disorders:

   Agitation, confusion, hallucination, illusion.

7. Blood: Anemia.

8. Renal system: Blood urea nitrogen elevated, oliguria.

9. Respiratory System: Apnea, bronchospasm, dyspnea, hypercapnia.

10. Vision Disorders: Photopsia, abnormal vision

7. REVIEW OF LITERATURE

1. Journal of clinical anaesthesiolgy and pharmacology.2010, 26(2).149-53. Dhurjoti prosad et al. Studied 90 children for caudal analgesia in age group between one to six years and divided into three groups. Group R received 0.25%of ropivacaine 1ml/kg , Group C received 0.25%of ropivacaine 1ml/kg with clonidine 1 mcg/kg and group D is received 0.25% of ropivacaine 1ml/kg with dexmedetomidine1mcg/kg. This study results concluded the duration of analgesia was 6 ± 0.46 hours in Group R , Group C is 13.17 ± 0.68 hours and Group D 15.26±0.86 hours.Addition of dexmedetomidine and clonidine with ropivacaine in caudal anaaethesia better than ropivacaine alone and without any hemodynamic instability.

2. Journal of acta anaeathesia scandinavica.2009.53 (2), 251-256. Boles, Saadway et al , studied the effect of dexmedetomidine combined with bupivacaine in caudal anaesthesia in children . In this study results were excellent intraoperative and postoperative analgesia and without any adverse effects.

3. British journal anaesthesia 2009, 103(2) .268-274. A M Abd Elwahab et al, studied 60 patients randomized selected age between 6 months to six years for infra umbilical surgeries. It is divided into two groups. Group C received bupivacaine 0.25% 1ml/kg with clonidine 2 mcg/kg and Group D received bupivacaine 0.25% 1ml/kg added with dexmedetomidine 2 mcg/kg in

caudal anaesthesia. This study showed that dexmedetomidine group had prolonged duration of post operative analgesia than the clonidine group, without any significant side effects.

4. Anaesthesia and analgesia 2007, 14.1356-1363.Thomas et al. a comparative study of single shot caudal epidural clonidine ,morphine and hydromorphine with ropivacaine in caudal anaesthesia in children age between 6 months to six years .It was a double blind randomized controlled study divided into three groups, clonidine 2mcg/kg, morphine 50mcg/kg, hydromorphine 10mcg/kg with 0.25%of ropivacaine in adrenaline. Results of in this study was clonidine combined with ropivacaine to produce the increases duration of analgesia without significant side effects. Caudal opioid produced the postoperative nausea and vomiting.

5. Peadiatric anaesthesiology 2005, vlume 15(7), page 580-585. Nursel et al. Comparison between clonidine and ketamine with ropivacaine in caudal anaesthesia for children .the randomized controlled study divided into three groups. Group R is received 0.75ml/kg of 0.25% ropivacaine . Group RC is received 0.75ml/kg of 0.25% ropivacaine with mcg/kg clonidine and Group RK is received 0.75ml/kg of 0.25% ropivacaine with ketamine 0.5mg /kg. All three groups monitored the insulin, glucose, cortisol, sedation levels and complications. Results of this study are clonidine and ketamine group is prolonged duration of analgesia and attenuate the stress response to surgery.

6. European journal of anaesthesia. 2010. 27, (11), 560. Erbek et al studied comparison between bupivacaine 0.5% and dexmedetomidine sedation for septoplasty procedure. The patients divided randomized into two groups. Group B patients received 0.5% bupivacaine alone and grooup BD patients received 0.5% bupivacaine with dexmedetomidine 2mcg/kg. Results of this study were bupivacaine combined with dexmedetomidine is better intraoperative, postoperative pain relief and reduce the intraoperative bleeding than bupivacaine alone.

7. Indian journal of anaesthesiology. 2010, 53(3) page 226-230. Jabir kaur et al. studied to determine the quantitative and qualitative of caudal epidural anaesthesia, hemodynamic effects and postoperative duration of analgesia. This is randomised controlled double blind study for children age between one to nine years divided into two group, group I received 0.25% of ropivacaine and group II received 0.25% of ropivacaine with clonidine 2mcg/kg .the results of this study is duration of analgesia in group II is prolonged the duration of postoperative analgesia and efficient intraoperative analgesia without significant hemodynamic changes.

8. Indian journal of anaesthesiology. 2009. 53(4) :450-459. Deepanjali pant et al studied forty children randomized selected and evaluated for caudal clonidine analgesic effects, hemodynamic effects and respiratory status of the children in day care pediatric surgeries. Divided into the two groups. Group B children are received 0.25%of bupivacaine 0.75ml and Group C are received

0.25% of bupivacaine 0.75ml with clonidine 2mcg/kg. Postoperatively monitoring for OPS score, sedation score, pulse rate and blood pressure were recorded. This study concluded that the duration of analgesia in group C was 10.25 hours compared with group B was 4.55 hours and without hemodynamic instability.

9. British journal of anaesthesia.2011. 106. N Kumar et al. This is randomized controlled prospective study was selected 50 patients for upper abdominal surgeries and divided into two groups. Group BM patients are received 0.25% of bupivacaine 1.25ml/kg with morphine 30mcg/kg and Group BC 0.25% of bupivacaine 1.25ml/kg with clonidine2 mcg/kg. In this study was concluded group BC was prolonged duration of post operative analgesia than group BM. The morphine group was produced more nausea and vomiting.

10. Journal of acta anaesthesia scandinavica 2006.50(4); 501-501.Korkmaz F et al. This is randomized, prospective, controlled study for prolong duration of analgesia for caudal clonidine combined with isobaric bupivacaine.Totaly sixty children was selected and divided into the two groups. Group B are received 1ml/kg of 0.125% isobaric bupivacaine and group BC are received1ml/kg of 0.125% isobaric bupivacaine with 2mcg/kg of clonidine. Results in this study the duration of analgesia prolonged in bupivacaine with clonidine 650 minutes without significant hemodynamic instability for intraoperative and postoperative periods

11. Indian journal of anaesthesiology 2011, 55.226-230. Vijay anand G et al.The prospective ,randomized controlled , double blind study wre to comparison of caudal 0.25% of isobaric ropivacaine with dexmedetomidine undergoing lower abdominal surgeries in sixty children age between six months to six years ,divided into two groups. Group R are received 0.25% of ropivacaine 1ml/kg and group RD are received 0.25% of ropivacaine 1ml/kg with dexmedetomidine 2mcg/kg. Concluded from in this study the duration of postoperative analgesia in group RD was 14.5hours compare than group R was 5.5 hours without any hemodynamic instability.

8. MATERIALS AND METHODS

This Prospective, randomised, double blind, comparitive study was done to compare the efficacy and safety of dexmeditomidine and clonidine as ajuvants to caudal ropivacaine in postoperative analgesia for children. The study was carried out in 60 children at Government Rajaji hospital, Madurai for surgeries of lower abdomen and perineum in the year 2012. The children in the age group of 1-6 years and weighing 5-20Kgs were selected for the study.

INCLUSION CRITERIA:

Elective infra umbilical surgeries

Both sexes

Age: Between one to six years.

ASA: I

Weight: 5-20kg

Exclusion CRITERIA:

1. Known allergic to LA.
2. Local sepsis.
3. Neurological diseases.
4. Bleeding disorders.
5. Skeletal deformities

Only ASA I physical status patients were chosen to avoid the influence of the associated diseases. The sixty children were divided into two groups of thirty each.

Group RC: Received 1ml/kg of 0.25% ropivacaine and 1μg/ kg clonidine. Group RD: Received 1ml/kg of 0.25% ropivacaine and 1 μg/ kg dexmedetomidine.

Pre anaesthetic evaluation

1. History.
2. Clinical examination.
3. Relevant investigations – haemoglobin, urine analysis.
4. Informed consent from parents.
5. All children were kept nil per oral for 6 hrs prior to surgery.

Children premedicated with 0.5mg/kg of oral midazolam 45 minutes before anaesthetic procedures. On arrival in the operation theatre, routine monitors (ECG, pulse oxymetry, NIBP) were attached and baseline vital parameters like mean arterial blood pressure (MAP), heart rate(HR) and arterial oxygen saturation (SPO2) were recorded. Induction was done by increasing concentration of sevoflurane (3 -8 %) along with oxygen and nitrous oxide mixture (40:60) through ayres T piece with Jackson Rees modification and facemask. After induction, an intravenous line was secured. Injection atracurium 0.5 mg / kg was administered to facilitate endotracheal intubation with appropriate size endotracheal tube.

Anaesthesia was maintained with 60%, nitrous oxide in40% oxygen and 0.6%.Sevoflurane using controlled ventilation. The patients were positioned in left lateral position. After aseptic draping, a 23G needle was introduced into caudal space and either or ropivacaine with clonidine (Group RC) or ropivacaine with dexmedetomidine (group RD) was administered. At the end of the operation, residual neuromuscular block was reversed by appropriate doses of neostigmine 40µg/kg & atropine 10µg/kg and tracheal extubation was performed. Postoperatively they were monitored in postanasthetic care unit. Pulse rate, MAP and SPO2 were recorded throughout the operation at an interval of five minutes

Intraoperative monitoring:

Pulse rate, blood pressure, saturation. Decrease of mean arterial blood pressure and pulse rate more than 30% from the baseline values were defined as severe hypotension and bradycardia, respectively which were treated injection atropine sulphate 20mcg/kg. At the beginning of skin closure anaesthesia was discontinued.

Postoperative monitoring was done in post anaesthetic care unit where vital parameters and pain, sedation scoring done every 15 minutes for 3 hours and then every one hour.

1. Time from caudal block to end of the surgery.
2. Sedation was assessed by 4 point scale.
3. Pain was assessed by cries scale.

4. Duration of post-op analgesia.
5. Pulse rate, map and spo2.
6. Complications.

The following parameters were assessed

4 point sedation scale:

1. Barely arousable. (Sleeps Needs shaking or shouting to arouse).
2. Asleep. (Eyes closed arousable with soft voice or light touch).
3. Sleepy. (Eyes open but less active and responsive).
4. Awake.

CRIES pain scale:

	0	1	2
Crying	No	High pitched	Inconsolable
Requires O2 for SPO2 >95%	No	< 30% of O2	> 30% of O2
Increased vital signs	No increase in HR and MAP	↑ HR or MAP < 20%	↑ HR or MAP > 20%
Expression	None	Grimace	Grimace/grunt
Sleepless	No	Wakes up at frequent intervals	Constantly awake

Score 0- signifies excellent analgesia.

Score 10- indicate ineffective analgesia.

Rescue analgesia with syrup paracetamol (15mg/kg) was given when the pain score was 4 or more.

9. STASTISTICAL ANALAYSIS

Statistical Tools (To be included at the end of Materials and Methods)

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

10. OBSERVATION AND RESULTS

The two groups were compared in characteristics like demographic data and basic vital parameters (pulse rate, MAP, saturation) and duration of surgery, duration of postoperative analgesia, complications.

Table-1 DEMOGRAPHIC VARIABLES

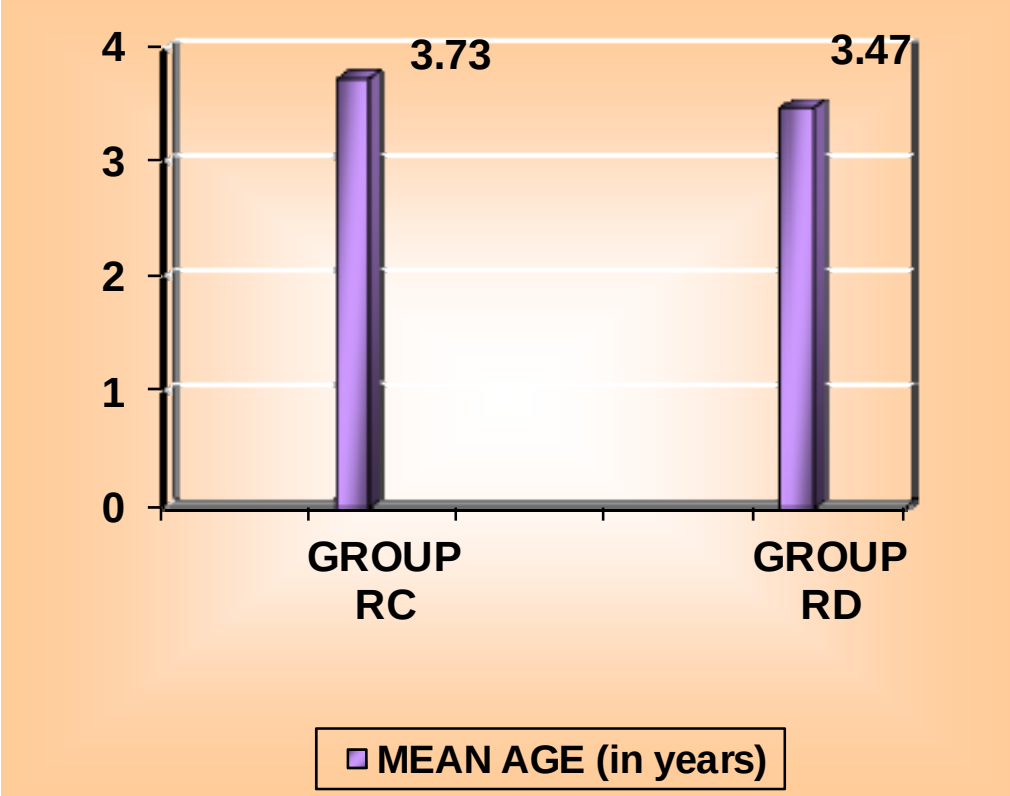
Variable	Group RD	Group RC	P	Significance
Age (years)	3.47	3.73	0.5283	Not significant
Sex Male Female	 25 5	 24 6	0.7408	Not significant
Weight (kg)	14.77± 3.57	15± 3.73	0.7608	Not significant

The mean age of children in group RD was 3.47 years and in group RC was 3.73 years which is found not to be statically significant with P value of 0.5283.

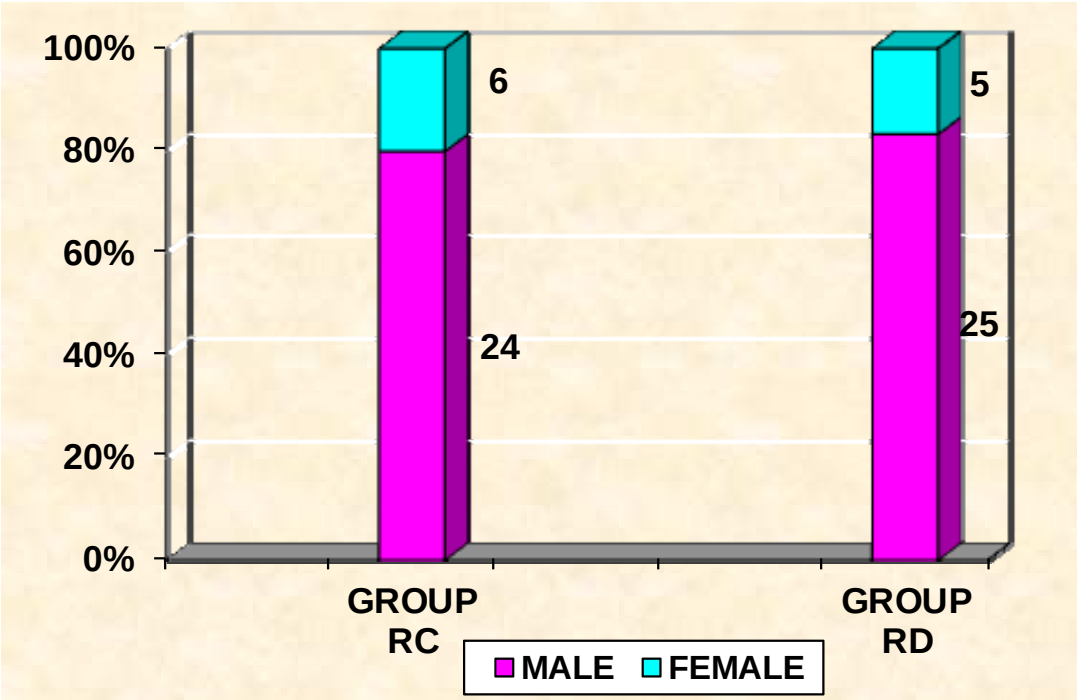
The sex distribution in group RD 25 males and 5females and in group RC were compared and found 24 males and 6 females. Both group were compared and found not to be statistically significant.

The mean weights of children were 14.77 ±3.57 kg in group RD and 15± 3.73 kg in group RC. Both group were compared and found not to be statistically significant.

GRAPH 1: AGE DISTRIBUTION



GRAPH 2: SEX DISTRIBUTION



GRAPH 3 : WEIGHT (KGS)

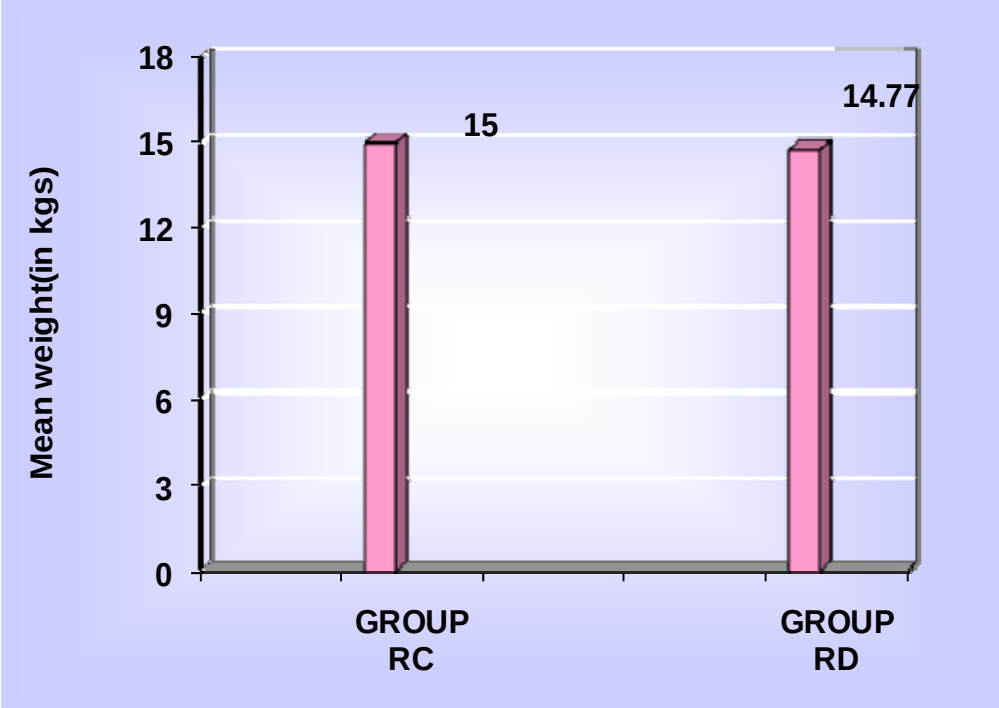
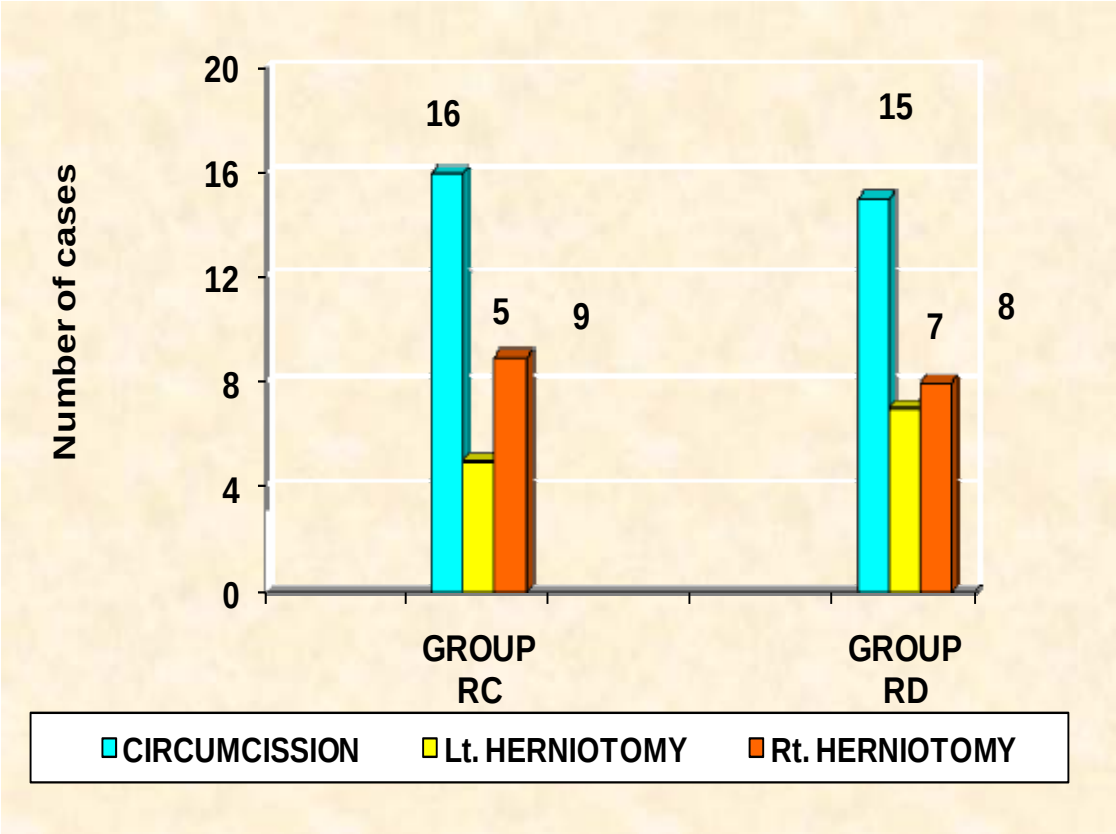


TABLE 2: PROCEDURE DONE

Procedure	Group RC		Group RD	
	No	%	No	%
Circumcission	16	53.3	15	50
Left Herniotomy	5	16.7	7	23.3
Right Herniotomy	9	30	8	26.7
Total	30	100	30	100

The procedures done in group RC herniotomy for 14 children and circumcission for 16 children . In group RD herniotomy for 15 children and circumcision for 15 children

GRAPH 4: PROCEDURE DONE



B: HAEMODYNAMIC CHANGES

Table 3: Preoperative, Intra operative and postoperative changes in pulse rate

Pulse rate	Pulse rate of				'p'
	Group RC		Group RD		
	Mean	SD	Mean	SD	
Pre op 0 hour	106.0	4.8	106.9	5.2	0.4399 Not significant
Intra op 5min	104.5	4.8	104.2	4.2	0.9289 Not significant
10 min	95.8	1.6	95.9		0.6476 Not significant
15 min	93.8	2.1	94.0		0.6644 Not significant
20 min	92.5	1.4	92.8		0.988 Not significant
25 min	92.5	1.9	92.1		0.2787 Not significant
30 min	92.3	1.6	91.8		0.2975 Not significant
45 min	91.3	1.4	91.1	1.3	0.5577 Not significant
Post op 60 minutes	91.2	1.7	90.9	1.4	0.6357 Not significant
75min	91.2	1.8	90.8	1.5	0.2985 Not significant
90 min	90.8	1.5	90.7	1.3	0.7373 Not significant
105 min	90.7	1.7	90.5	1.4	0.659 Not significant
120min	91.4	1.6	90.6	1.3	0.0476 Not significant

135min	90.5	1.4	90.4	1.3	0.7342 Not significant
150 min	90.4	1.4	90.4	1.4	1.0 Not significant
165 min	90.7	1.5	90.4	1.0	0.7111 Not significant
180 min	91.1	1.9	90.3	1.4	0.1023 Not significant
4 hours	90.7	1.7	90.5	1.4	0.659 Not significant
5 hours	91.4	1.6	90.6	1.3	0.0476 Not significant
6 hours	90.5	1.4	90.4	1.3	0.7342 Not significant
7 hours	90.4	1.4	90.4	1.4	1.0 Not significant
8 hours	90.7	1.5	90.4	1.0	0.7111 Not significant
9 hours	91.1	1.9	90.3	1.4	0.1023 Not significant
10 hours	93.4	1.8	90.6	1.5	0.0001Significant
11 hours	100.1	2.9	90.6	1.3	0.0001Significant
12 hours	103.0	3.3	90.3	1.2	0.0001Significant
13 hours	101.1	3.6	90.2	1.1	0.0001Significant
14 hours	102.8	3.4	90.4	0.9	0.0001Significant
15 hours	103.4	3.9	96.2	1.6	0.0001Significant
16 hours	104.1	4.4	99.7	2.2	0.0001Significant
17 hours	104.2	4.7	99.8	2.2	0.0001Significant

GRAPH 5: CHANGES IN PULSE RATE PRE,

INTRA, POST OPERATIVE PERIOD

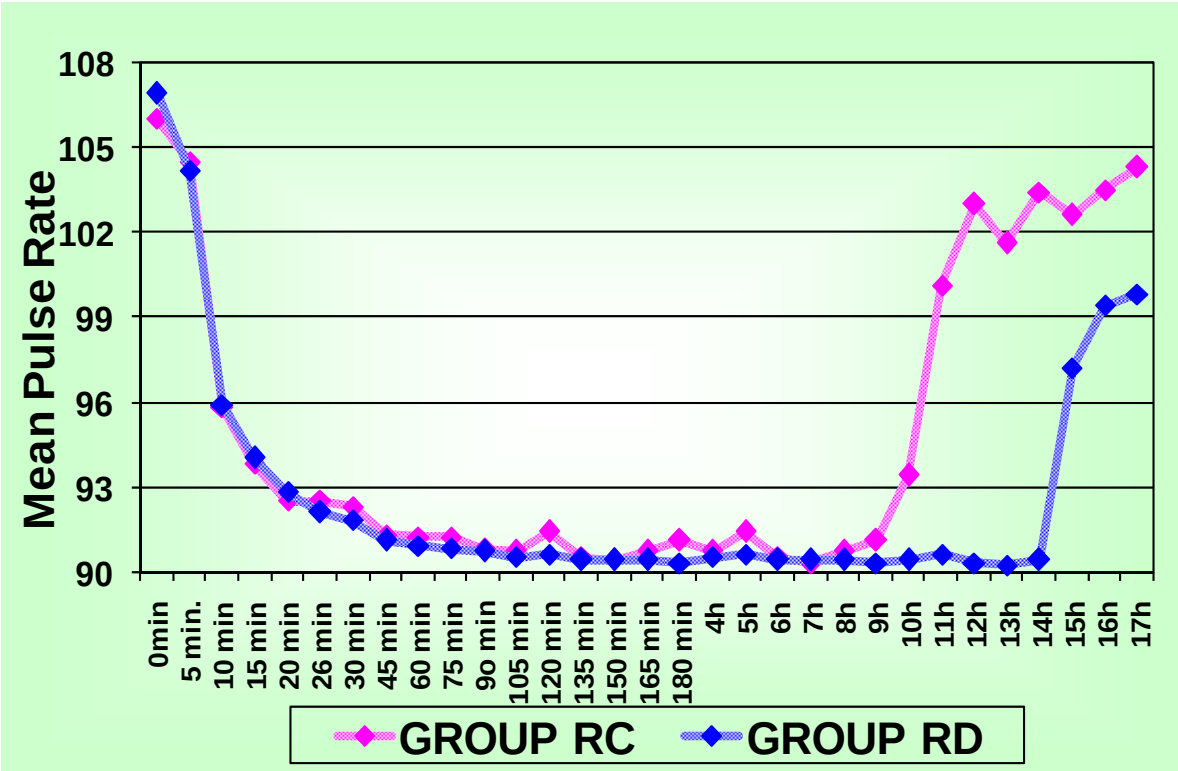


Table 4: Pre operative and intra operative, post operative changes in mean arterial pressure

MAP	MAP of				'p'
	Group RC		Group RD		
	Mean	SD	Mean	SD	
Pre op. 0min	85.7	3.7	84.7	3.1	0.3529 Not significant
Intra op 5min	81.3	2.3	80.5	1.7	0.1764 Not significant
10 min	75.4	1.8	74.7	2.1	0.2209 Not significant
15 min	74.4	1.9	74.8	1.8	0.3302 Not significant
20 min	73.8	1.4	74.0	1.5	0.8255 Not significant
25 min	74.2	1.1	74.4	1.2	0.7653 Not significant
30 min	73.0	1.2	73.3	1.1	0.3183 Not significant
45 min	73.0	0.9	73.0	0.9	0.8695 Not significant
Post op 60 minutes	73.1	1.0	72.9	0.9	0.5754 Not significant
75 minutes	73.0	1.0	72.9	0.9	0.6754 Not significant
90mins	72.9	0.8	72.8	0.8	0.5855 Not significant
105 min	72.9	1.0	72.7	0.9	0.3395 Not significant
120min	73.1	1.1	73.2	0.8	0.9319 Not significant
135 min	72.8	1.0	72.7	0.9	0.6701 Not significant

150min	72.7	0.8	72.8	0.7	0.6318 Not significant
165 min	73.0	0.9	73	0.7	0.9556 Not significant
180 min	72.8	0.9	72.9	0.9	0.9317 Not significant
4 hours	73.1	1.1	73.2	0.8	0.9319 Not significant
5 hours	72.8	1.0	72.7	0.9	0.6701 Not significant
6 hours	72.7	0.8	72.8	0.7	0.6318 Not significant
7 hours	73.0	0.9	73	0.7	0.9556 Not significant
8 hours	72.8	0.9	72.9	0.9	0.9317 Not significant
9 hours	72.7	0.9	72.6	0.7	0.6499 Not significant
10 hours	72.8	1.0	72.7	0.9	0.6701 Not significant
11 hours	72.7	0.8	72.8	0.7	0.6318 Not significant
12 hours	73.0	0.9	73	0.7	0.9556 Not significant
13 hours	81.6	3.2	72.5	0.9	0.0011Significant
14 hours	82.3	2.7	74.9	1.2	0.0001Significant
15 hours	82.1	2.9	78.3	0.8	0.0001Significant
16 hours	84.0	2.8	81.8	2.4	0.0011Significant
17 hours	85.6	3.3	82.8	2.5	0.0001Significant

GRAPH 6: MEAN ARTERIAL PRESSURE

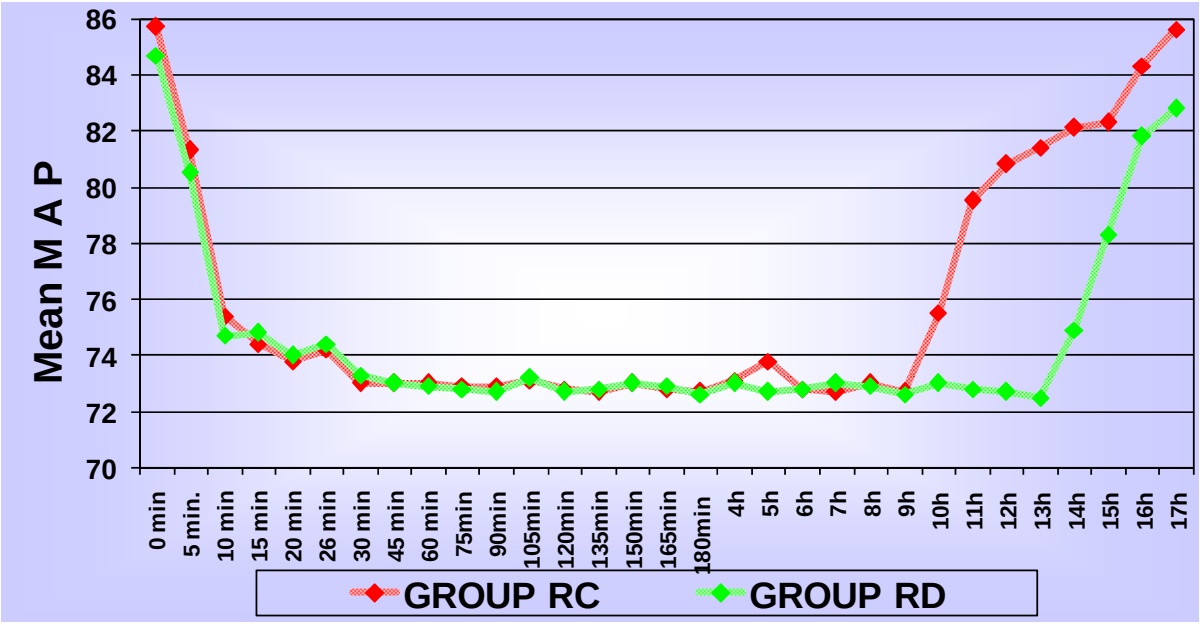


Table 3 & 4

The hemodynamic changes of Pulse rate and mean arterial pressure between both groups were compared in preoperative, intra operative and postoperative periods and significant changes were found only at 9^{th} to 17^{th} hours.

Table 5: Pre operative and Intra operative changes in SPO2

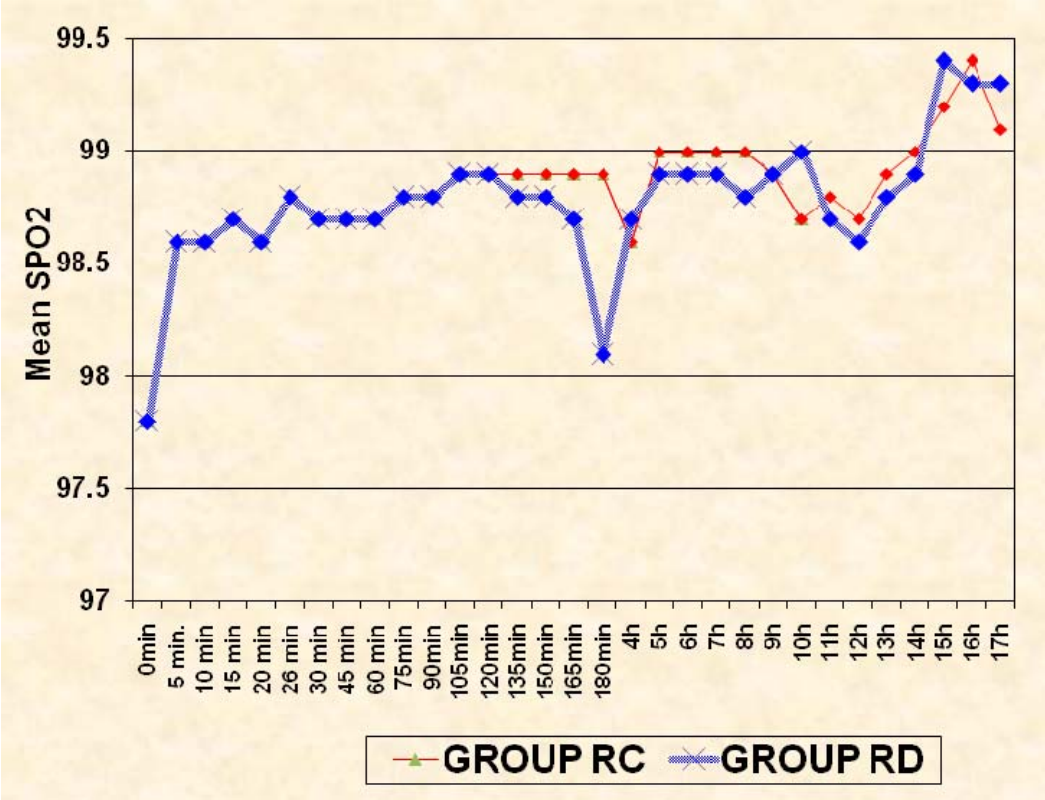
SPO2	SPO2				'p'
	Group RC		Group RD		
	Mean	SD	Mean	SD	
Pre op. 0 hour	97.8	1.1	97.6	1.1	1.0Notsignificant
Intra Op 5 min	98.6	0.5	98.4	0.4	1.0 Not significant
10 minutes	98.6	0.5	98.3	0.4	1.0 Not significant
15 minutes	98.7	0.5	98.7	0.5	1.0 Not significant
20 minutes	98.6	0.5	98.5	0.4	1.0 Not significant
25 minutes	98.8	0.4	98.7	0.4	1.0 Not significant
30 minutes	98.8	0.5	98.5	0.4	1.0 Not significant
45 minutes	98.6	0.4	98.7	0.5	1.0 Not significant
60 minutes	98.7	0.4	98.4	0.4	1.0 Not significant
75min	98.7	0.4	98.4	0.4	1.0 Not significant
90min	98.8	0.4	98.6	0.4	1.0 Not significant
105 min	98.8	0.4	98.5	0.4	1.0 Not significant
120MIN	98.9	0.3	98.6	0.3	1.0 Not significant
135min	98.9	0.3	98.6	0.3	1.0 Not significant
150 min	98.9	0.3	98.8	0.3	1.0 Not significant
165min	98.9	0.3	98.5	0.3	1.0 Not significant
180min	98.9	0.3	98.4	0.3	1.0 Not significant

Table 5 (a) Post operative changes in SPO2

Post op. SPO2 at	Post operative SPO2 of				'p'
	Group RC		Group RD		
	Mean	SD	Mean	SD	
4 hours	98.9	0.3	98.8	0.2	1.0 Not significant
5 hours	98.9	0.3	98.7	0.2	1.0 Not significant
6 hours	98.9	0.3	98.8	0.2	1.0 Not significant
7 hours	98.9	0.3	98.7	0.3	1.0 Not significant
8 hours	98.9	0.3	98.6	0.3	1.0 Not significant
9 hours	98.9	0.3	98.8	0.3	1.0 Not significant
10 hours	99.6	0.2	99.4	0.2	1.0 Not significant
11 hours	99.4	0.2	99.3	0.2	1.0 Not significant
13 hours	98.9	0.3	98.7	0.3	1.0 Not significant
14 hours	99.0	0.2	98.9	0.3	1.0 Not significant
15 hours	99.2	0.2	99.2	0.2	1.0 Not significant
16 hours	99.4	0.3	98.9	0.3	1.0 Not significant
17 hours	99.0	0/2	98.9	0.3	1.0 Not significant

The saturation was compared between both groups pre operative, intra operative and post operative period were compared and found not to be statistically significant.

GRAPH 7: SPO2


99.5
99
98.5
98
97.5
97
Mean SPO2
0min
5 min.
10 min
15 min
20 min
26 min
30 min
45 min
60 min
75min
90min
105min
120min
135min
150min
165min
180min
4h
5h
6h
7h
8h
9h
10h
11h
12h
13h
14h
15h
16h
17h
GROUP RC
GROUP RD

C: COMPARATIVE EFFICACY

Table 6: Duration of surgery

Parameter	**Duration of surgery (in minutes)**	
	Group RC	**Group RD**
Range	20-45	20-45
Mean	31.0	30.0
SD	8.14	7.88
'p'	0.6244 Not significant	

Table 6

The mean duration of surgery in group RD was 31 minutes and RC 30 minutes, which was found not to be statistically significant.

GRAPH 8: DURATION OF SURGERY

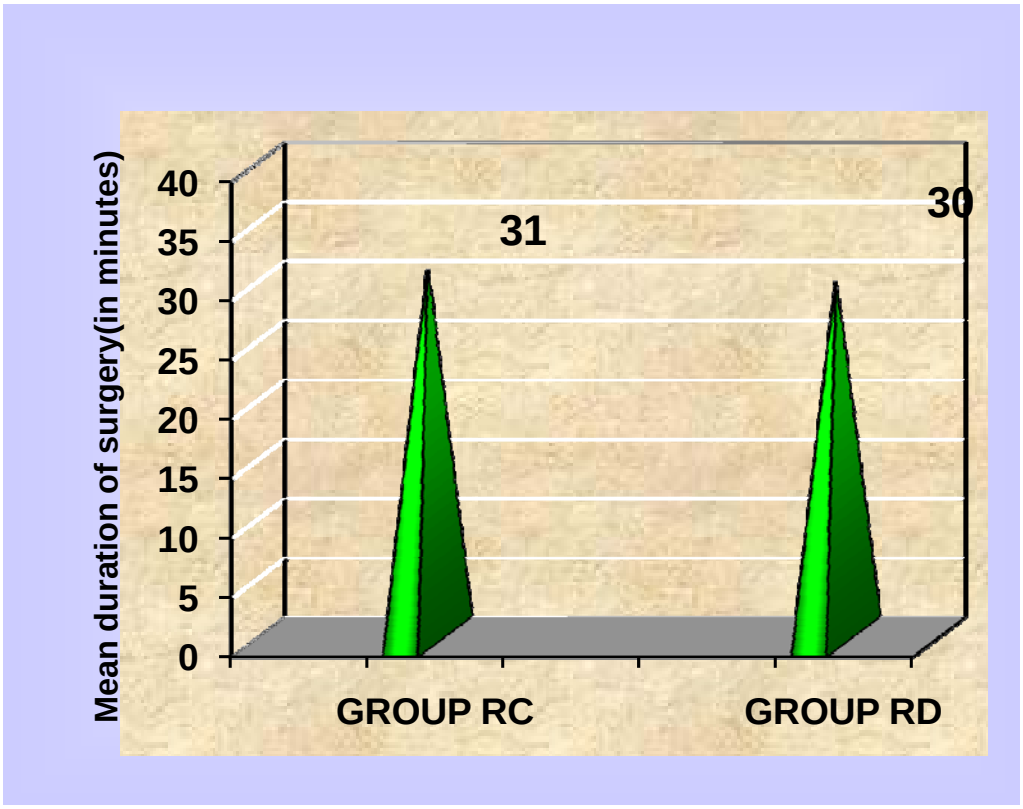


Table 7: Duration of postoperative analgesia

Parameter	**Duration of Post Operative analysis (in hours)**	
	Group RC	**Group RD**
Range	8-12	13-17
Mean	9.8	14.67
SD	1.4	1.15
'p'	0.0001 Significant	

Table 7

The mean duration of post-operative analgesia was 14.67±1.4 hours in group RD and 9.8±1.15 hours in group RC. Both group were compared and found that dexmedetomidine group had a longer duration of postoperative analgesia,which is statistically significant.

GRAPH 9: DURATION OF POSTOPERATIVE ANALGESIA

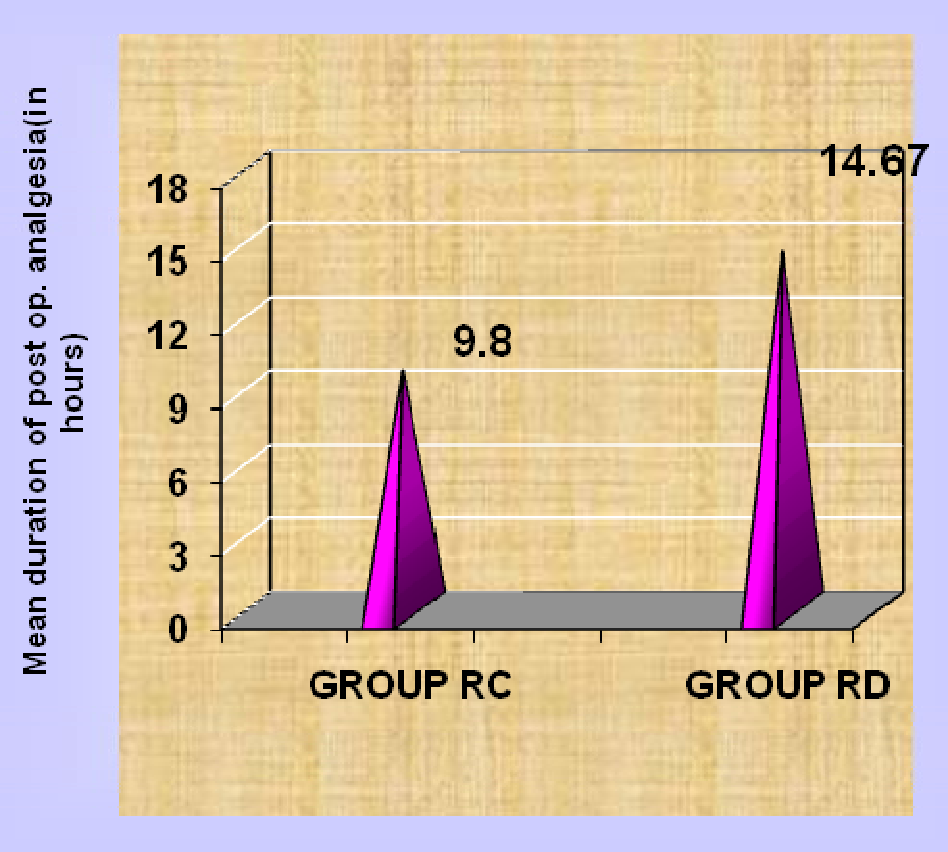
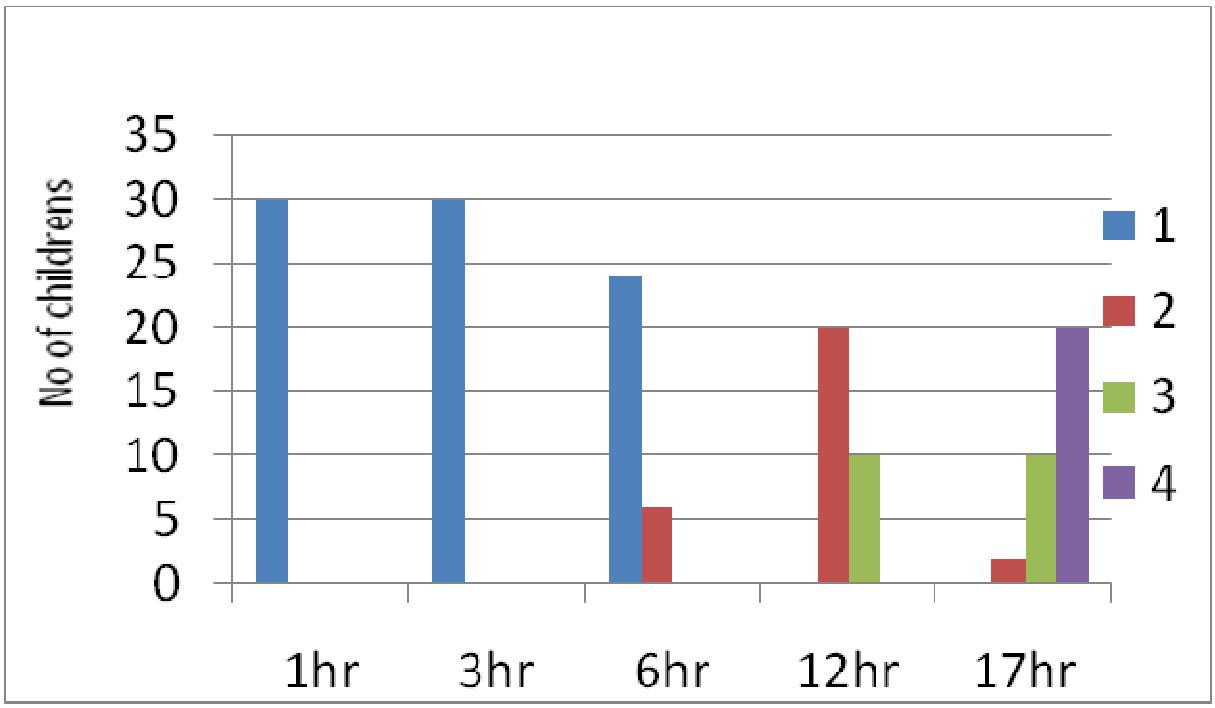


TABLE 8 : 4 POINT SEDATION SCORE

TIME IN HOURS	GROUP RD				GROUP RC			
	1	2	3	4	1	2	3	4
1hr	30	0	0	0	30	0	0	0
3hr	30	0	0	0	25	5	0	0
6hr	24	6	0	0	18	10	2	0
12hr	0	20	10	0	0	15	12	3
17hr	0	0	10	20	0	0	8	22
P VALUE 1.0 NOT SIGNIFICANT								

The Sedation score was compared between GROUP RD & GROUP RC in postoperative periods and found not to be statistically significant.

GRAPH:10 GROUP RD SEDATION SCORE



GRAPH 10a: GROUP RC SEDATION SCORE

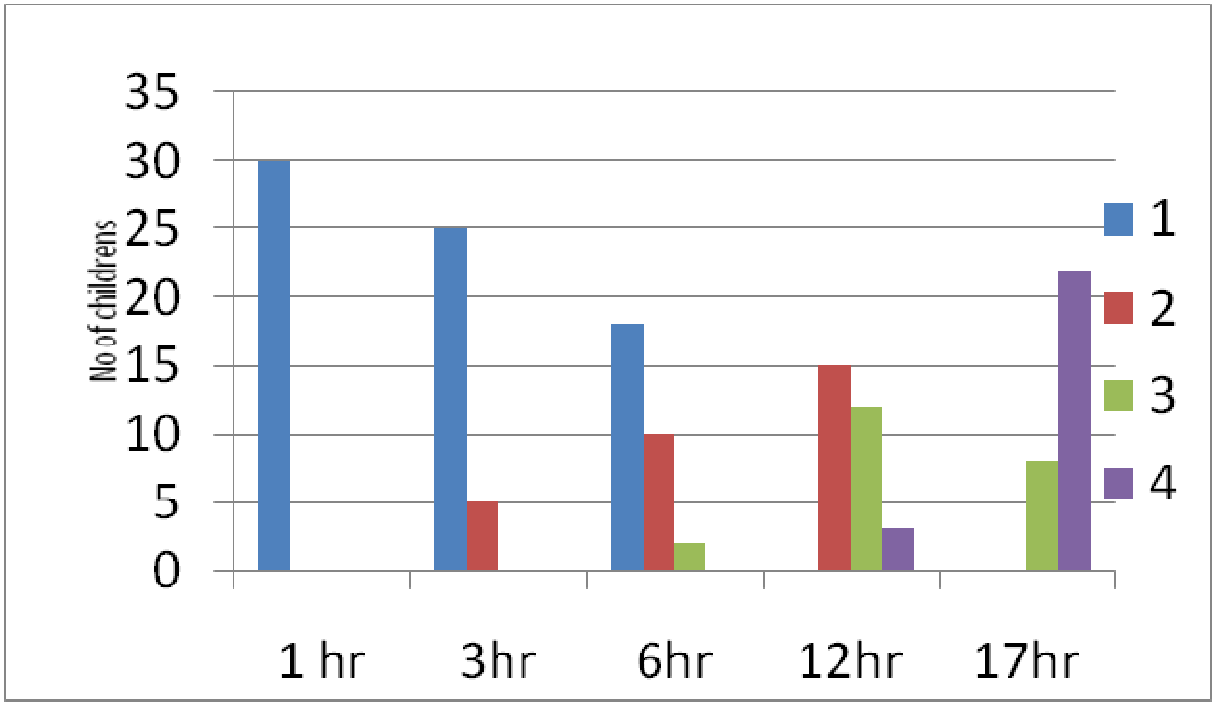


Table 9: CRIES Pain scale

Pain scale	Group RC		Group RD	
	No	%	No	%
0	14	46.7	20	66.7
1	15	50	10	33.3
2	1	3.3	-	-
Total	30	100	30	100
Range	0-2		0-1	
Mean	0.57		0.33	
SD	0.57		0.48	
'p'	0.1039 Not significant			

The CRIES pain scale was compared between two groups and found not to be statistically significant.

GRAPH 11: CRIES PAIN SCALE

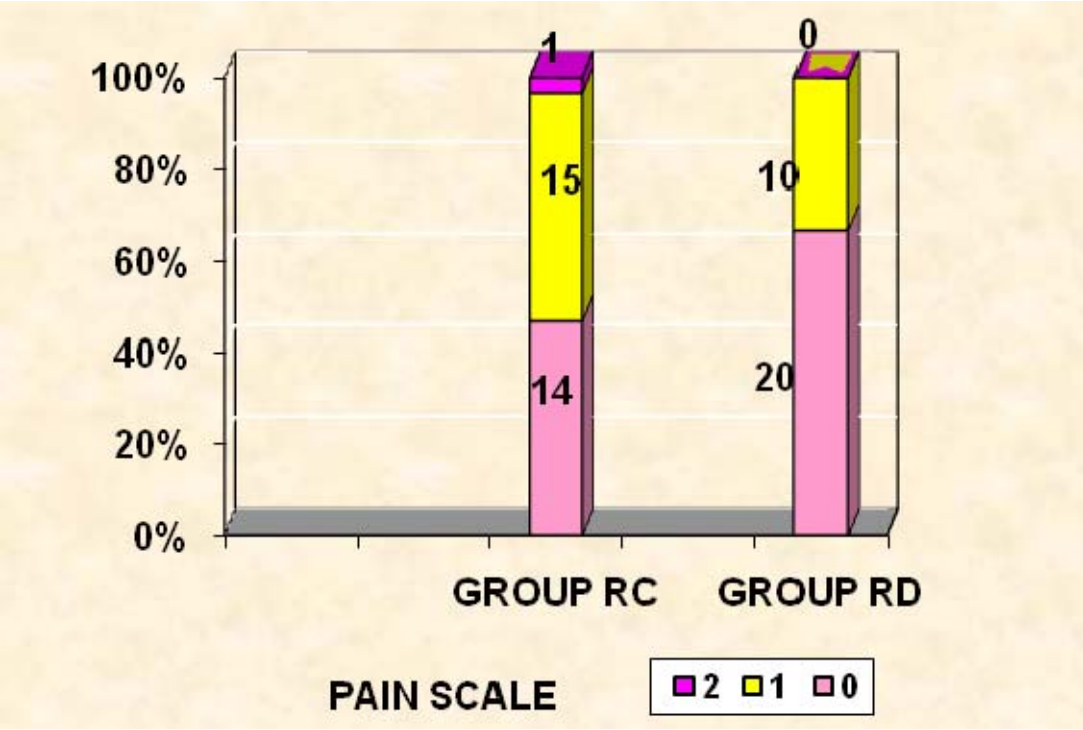
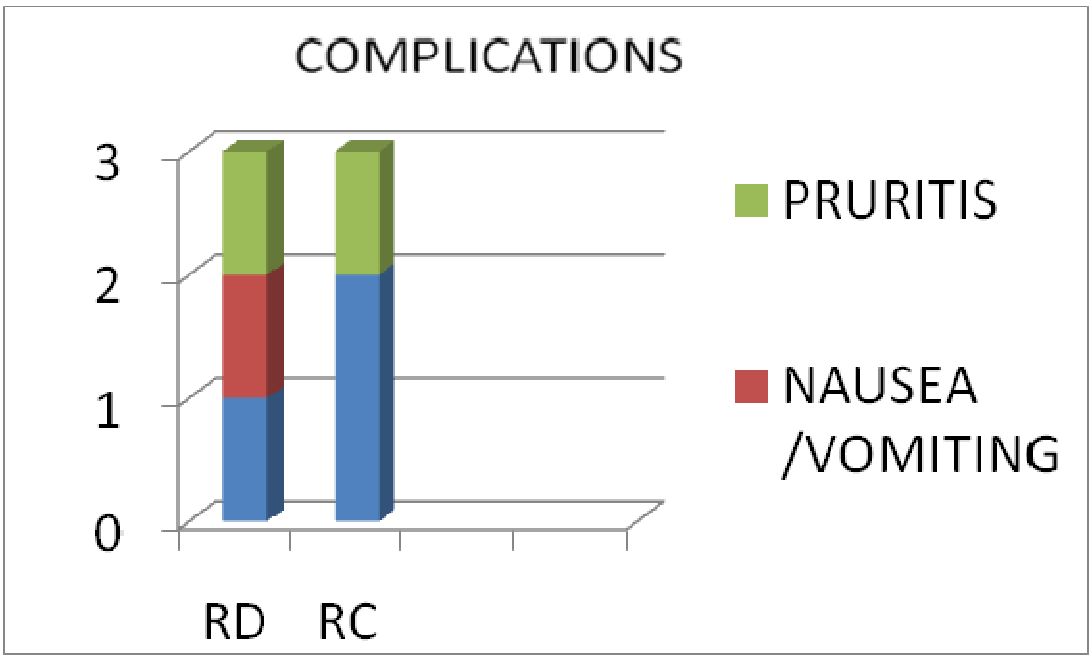


Table 10 : Complications

Complications	Group RC		Group RD	
	No	%	No	%
Nausea	1	3.3	2	6.7
Nausea & Vomiting	1	3.3	-	-
Pruritis	1	3.3	1	3.3
Nil	27	90	27	90
Total	30	100	30	100
'p'	1.0 Not significant			

The complications in two groups were compared and found not to be statistically significant.

GRAPH 12: COMPLICATIONS



11. DISCUSSION

Postoperative analgesia provides not only pain relief but also inhibits trauma induced nociceptive impulses to blunt autonomic reflexes. It allows the patients to breath and move freely to enhance early restoration of function.

Untreated postoperative pains produce the several detrimental acute and chronic effects. Neuroendocrine responses to pain result in increases sympathetic tone, increased catecholamine and catabolic hormone secretions and decreased secretion of the anabolic hormones.

The neuroendocrine stress response may potentiate to other detrimental physiological effects like hypercoagulability, immunosuppressant, and delay in return of gastrointestinal function. Decreased postoperative respiratory function is markedly especially after abdominal and upper thoracic surgeries. Children with poor postoperative pain control may breathe less deeply have an inadequate cough and be more susceptible to the development of post operative pulmonary complications. Inadequate postoperative pain relief produce the long term consequences like that eating disturbance, altered the sleeping pattern and increased pain perception during subsequent painful experiences.

The benefits of paediatric regional analgesia for children include safety, and efficacy with no increased risk when compared with general anaesthesia alone but requires technical expertise. Children should faster recovery, shorter hospital ICU stay , and reduced ventilator requirement when supplemented with

regional anaesthesia .the spectrum of autonomic ,hormonal, metabolic, immunologic/inflammatory, and neurobehavioral consequences caused due to surgical stress can be decreased by regional anaesthesia.

Benefits of regional anaesthesia is not only pain relief it also reduction of general anaesthetic requirement ,may reduce the toxicity of general anaesthetic agents, reduce the neurohormonal stress responses ,improve the gastrointestinal functions, reduction of intraoperative blood loss and improve the defence mechanisms.

Enteral and parenteral analgesics used in postoperative analgesia, are associated side effects like gastrointestinal bleeding, nausea and vomiting, sedation, precipitation of asthma tic attack, respiratory depression, thrombocytopenia and nephrotoxicity , hepatotoxicity, etc.

Several local anaesthetic agents like lidocaine, bupivacaine and ropivacaine have been used for caudal block. Adjuvants like opioids , clonidine, dexmedetomidine, midazolam and ketamine are added to local anaesthetic agents to the duration of analgesia was increased, decrease the individual dose of the drug and thereby decreasing the side effects.

Dexmedetomidine and Clonidine is an effective adjuvant to local anaesthetic agents when administered for caudal block. Addition of both has been found to increase the duration of analgesia without any increase in the side effects. When administered caudally, both produces analgesia by interacting with alpha 2 adrenergic receptors. These receptors are located on the superficial

laminae of spinal cord and brain stem nuclei implicated in pain, so analgesia can be produced at peripheral, spinal and brain stem sites.

Ideal anaesthetic technique should be targeted at three sites periphery, sensory flow in nerves and cells in the central nervous system. The administration of an analgesic before any tissue damage takes place could interfere with and reduce the magnitude of nociception and thereby prevent a state of hypersensitisation.

The various methods of providing pain relief have some side effects whichprohibit their use, for eg, narcotics in children, because of their respiratory depression, the objection to needles in the case of parenterally administered analgesics.

Caudal anaesthesia was chosen for this study as it is the simplest and safest techniques in paediatric surgery with a success rate of single shot caudal epidural injection of local anaesthetic agents and additives that prolong the postoperative analgesia. By this regional technique, problems and complications of intubation and polypharmacy due to general anaesthesia are avoided.

In this study, we used clonidine and dexmedetomidine was used in the dose of 1µg /kg along with 0.25% ropivacaine and did not observe significant incidence of adverse effects like hypotension, bradycardia and respiratory depression,

Lee et al. This study administered clonidine dose of 2µg /kg along with bupivacaine in children undergoing lower limb orthopaedic surgery in their

study. They observed higher incidence of bradycardia and hypotension associated with 2μg /kg dose of clonidine added to bupivacaine.

The two groups were compared with respect to weight, sex, age, and, duration of post operative analgesia, duration of surgery, complications. The pre operative, intra and postoperative pulse rate, mean arterial pressure and saturation and complication were also compared.

SEDATION:

Sedation and hence patient comfortability as assessd from 4 point sedation score. It was not significant in both groups.

ANALGESIA:

Pain intensity was assessed in this study by CRIES scale. This scale is a reliable and a sensitive tool for evaluvation of postoperative pain in children.

The mean duration and SD of analgesia for caudal RC was 9.8 ± 1.4hours. In group RD mean duration and SD of analgesia was 14.67± 1.15 hours.

The results of the study done by Mausumi Neogi et al. Journal of Anaesthesia and Clinical Pharmacology 2010; 26(2): 149-153 results of the mean duration of analgesia was 6.32±0.46 hours in group Ropivacaine, 13.17±0.68 hours in group Clonidine and 15.26±0.86 hours in group Dexmedetomidine. The prolongation of duration of analgesia was significant in both group clonidine and dexmedetomidine was compared to group ropivacaine.

Vijay anand et al .Indian journal of anaesthesia 2011,55:226-230. Results of this study duration of postoperative analgesia in ropivacaine combined with demedetomidine is14.5±0.5hours than ropivacaine group is 5.5±0.5 hours and less emergence agitation following sevoflurane inhalation anaesthesia.

HAEMODYNAMIC STABILITY:

In both the groups there was not significant alteration in the intra operative and Postoperative pulse rate, mean arterial pressures and saturation. The difference found at 9^{th} to 17^{th} hours of post operative period pulse rate, mean arterial pressures was significant because of group RD was increase duration of analgesia and comportability better than clonidine group. But both group does not cause any hypotension bradycardia and respiratory depression.

COMPLICATION:

There were no significant complications in both groups were noted.

12. SUMMARY

This study was carried out at Government Rajaji hospital, Madurai, in 60 children between one to six years of age with ASA physical status I grading, the procedure underwent by children were infraumblical surgeries. They were divided into the two groups of thirty each group. Group RC (1ml/ kg of 0.25% ropivacaine and 1μg/ kg clonidine), Group RD (1ml/kg of 0.25% ropivacaine and 1 μg/ kg dexmedetomidine) as above. All children were given general anaesthesia and maintained with sevoflurane 0.6% and 60% N_2O in 40% O_2 and atracurium. This study showed that

1. Dexmedetomidine when added with caudal ropivacaine provided longer duration of analgesia than Clonidine with ropivacaine .
2. Patient comfortability in terms of sedation and duration of analgesia was better in dexmedetomidine group than clonidine group.
3. Cardiovascular stability was similar in both the groups.
4. There were no significant complications in both groups.

13. CONCLUSION

From this study it is concluded that dexmeditomedine added to ropivacaine in caudal anaesthesia appears to provide efficious pain relief and comfortability for longer duration than clonidine added to ropivacaine in children undergoing infraumblical surgeries without any significant side effects.

BIBLIOGRAPHY

1. Anatomy for Anaesthetists- Harold Ellis 8th Edition. Page: 107-118.
2. Textbook of Medical Physiology-Arthur C.Guyton.6th Edition.page: 600-609.
3. Epidural Analgesia-philip R.Bromage: Page: 258-282.
4. Text book of pain – Wall & Melzacks, 5th Edition.
5. Understanding paediatric anaesthesia- Rebecca Jacob.2nd Edition. Page: 106-9.
6. Neural blockade in clinical anaesthesia and management of pain- Michael. J. Cousins &Phillip.O. Briden baugh: 3rd edition.Page:323-342.
7. Miller"s Anaesthesia- Ronald D. Miller. 7th edition.
8. Ropivacaine - J.H McCLURE. British journal of Anaesthesia1996, 76: 300-7.
9. Clonidine in peadiatrics- Sujatha basker et al.Indian joural of anaesthesia 2009; 53 (3):270-80.
10. Caudal ropivacaine and dexmedetomidine in children for lower abdominal surgery. Anand et al- Indian journal of anaesthesia 2011; 55.Page:340-6.
11. Addition of clonidine or dexmedetomidine to bupivacaine prolonged in caudal analgesia for children. A. M. Abd El wahab, et al. British journal of anaesthesia 2009,103 (2):Page: 268–74.
12. Caudal clonidine and ropivacaine better postoperative analgesia in peadiatrics. Kaur J et al. Indian journal of anaesthesia 2010, 4.Page: 226-230.

STUDY PROFOMA

Comparative study of Clonidine and Dexmedetomidine as Adjuncts to Ropivacaine in Caudal Analgesia in children.

NAME: AGE: SEX: WT:

DIAGNOSIS: SURGERY:

INFORMER:

Pre op:

PR - BP - SPO2 –

General Anaesthesia:

Induction – sevoflurane 3- 8% with oxygen and nitrous oxide mixture (40:60). After induction, Inj atracurium 0.5 mg/ kg was given for intubation. Maintainance with 60% N2O, 40% O2.and sevoflurane 0.6%

Caudal block:

Group RC: 1ml / kg of 0.25% ropivacaine and 1 mcg/kg clonidine .

Group RD: 1ml/kg of 0.25% ropivacaine and 1 mcg/kg dexmedetomidine .

Monitoring:

	5 min	10	15	20	25	30	35	40	45
HR									
MAP									
Spo2									

Time of caudal block -

Time from caudal block to end of surgery –

Sedation was assessed by 4 point sedation scale.

1. Barely arousable. (Sleep, Needs shaking or shouting to arouse)

2. Asleep. (Eyes closed, Arousable with soft voice or light touch)

3. Sleepy. (Eyes open but less active and responsive)

4. Awake.

Pain assessed by CRIES pain scale

	0	**1**	**2**
Crying	No	High pitched	Inconsolable
Requires O2 for SPO2 >95%	No	Less than 30% of O2	More than30% of O2
Increased vital signs	No ↑ HR and MAP	↑ HR or MAP < 20%	↑HR or MAP > 20%
Expression	None	Grimace	Grimace and grunt
Sleepless	No	Wakes frequent intervals	Awake

Duration of Postoperative analgesia:

Complication:

GROUP-RD

S.NO	NAME	AGE/SEX	WT.(KG)	IP NO	DIAGNOSIS	PROCEDURE	DURATION OF SURGERY	DURATION OF POST OPERATIVE ANALGESIA	Sedation score					PAIN SCALE	COMPLICATION
									1hr	3hr	6hr	12hr	17hr		
1	MASILAMANI	2/Mch	11	11124	PHIMOSIS	CIRCUMCISSION	25	15	1	1	1	2	3	0	NIL
2	SINDU	4/Fch	16	11326	LT. INGUINAL HERNIA	LT. HERNIOTOMY	35	13	1	1	1	3	4	0	NIL
3	KANDASAMY	3/Mch	14	10136	LT. INGUINAL HERNIA	LT. HERNIOTOMY	35	14	1	1	1	2	4	0	NIL
4	VIGNESH	1/Mch	10	10568	PHIMOSIS	CIRCUMCISSION	20	14	1	1	1	2	3	1	NIL
5	SATISH	5/Mch	19	12476	RT. INGUINAL HERNIA	RT. HERNIOTOMY	40	15	1	1	1	2	3	0	NIL
6	MARIMUTHU	6/Mch	20	12543	RT. INGUINAL HERNIA	RT. HERNIOTOMY	45	13	1	1	1	3	4	0	PRURITUS
7	SARANRAJ	3/Mch	14	13456	PHIMOSIS	CIRCUMCISSION	20	14	1	1	2	2	3	1	NIL
8	NAGARAJ	5/Mch	18	16789	PHIMOSIS	CIRCUMCISSION	25	15	1	1	1	3	4	0	NIL
9	UDAYAKUMAR	2/Mch	12	17654	PHIMOSIS	CIRCUMCISSION	25	16	1	1	1	2	4	1	NIL
10	SHANMUGAVEL	6/Mch	19	17658	LT. INGUINAL HERNIA	LT. HERNIOTOMY	45	16	1	1	2	2	4	0	NIL
11	SANKARI	3/Fch	14	18673	RT. INGUINAL HERNIA	RT. HERNIOTOMY	40	13	1	1	1	3	4	0	NIL
12	KRISHNASAMY	5/Mch	19	18345	PHIMOSIS	CIRCUMCISSION	35	14	1	1	1	2	4	1	NIL
13	KARTHIKA	4/Fch	16	18961	LT. INGUINAL HERNIA	LT. HERNIOTOMY	30	15	1	1	2	2	3	0	NIL
14	BALAJI	6/Mch	19	19043	PHIMOSIS	CIRCUMCISSION	25	13	1	1	1	3	4	0	NIL
15	PRABU	1/Mch	9	18921	PHIMOSIS	CIRCUMCISSION	20	13	1	1	1	2	4	0	NIL
16	KARTHIKEYAN	4/Mch	15	19563	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	16	1	1	1	2	3	1	NIL
17	ARUN	2/Mch	11	20948	RT. INGUINAL HERNIA	RT. HERNIOTOMY	45	15	1	1	1	2	3	0	NIL
18	SARANYA	4/Fch	17	22163	LT. INGUINAL HERNIA	LT. HERNIOTOMY	25	16	1	1	1	3	4	1	NIL
19	KALAIVANI	1/Fch	8	23212	RT. INGUINAL HERNIA	RT. HERNIOTOMY	30	14	1	1	2	2	4	0	NIL
20	TAMILARASAN	6/Mch	20	22478	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	15	1	1	2	2	4	1	NAUSEA
21	ANTHONY	3/Mch	14	25983	PHIMOSIS	CIRCUMCISSION	20	15	1	1	2	3	4	0	NAUSEA
22	NARESH	4/Mch	17	22314	RT. INGUINAL HERNIA	RT. HERNIOTOMY	30	15	1	1	1	3	4	1	NIL
23	SUNDARARAJAN	2/Mch	11	27612	PHIMOSIS	CIRCUMCISSION	25	17	1	1	1	2	4	1	NIL
24	RAHIM	5/Mch	19	23317	PHIMOSIS	CIRCUMCISSION	30	14	1	1	1	2	3	0	NIL
25	KRISHNAN	3/Mch	15	22456	PHIMOSIS	CIRCUMCISSION	20	14	1	1	1	2	3	0	NIL
26	RAMANATHAN	4/Mch	16	24590	LT. INGUINAL HERNIA	LT. HERNIOTOMY	35	16	1	1	1	3	4	0	NIL
27	GIRISH	1/Mch	9	23762	PHIMOSIS	CIRCUMCISSION	25	14	1	1	1	3	4	0	NIL
28	KAMESH	4/Mch	16	24982	PHIMOSIS	CIRCUMCISSION	20	15	1	1	1	2	4	0	NIL
29	VENKATESAN	3/Mch	13	25974	PHIMOSIS	CIRCUMCISSION	30	17	1	1	2	2	4	1	NIL
30	DINESH	2/Mch	12	26518	LT. INGUINAL HERNIA	LT. HERNIOTOMY	30	14	1	1	1	2	3	0	NIL

GROUP-RC

S.NO.	NAME	AGE/SEX	WT.(KG)	IP NO	DIAGNOSIS	PROCEDURE	DURATION OF SURGERY(MINS)	DURATION OF POST-OPERATIVE ANALGESIA(HRS	sedation score					PAIN SCORE	COMPLICATION
									1hr	3hr	6hr	12hr	17hr		
1	ESAKI RAJA	3/Mch	14	10484	PHIMOSIS	CIRCUMCISSION	25	10	1	1	1	2	3	0	NIL
2	JEGAN	5/Mch	18	12022	PHIMOSIS	CIRCUMCISSION	30	11	1	1	1	2	4	0	NIL
3	MANOJ	2/Mch	11	13130	RT.INGUINAL HERNIA	RT. HERNIOTOMY	45	12	1	1	1	2	3	0	NIL
4	ARAVIND	4/Mch	17	12569	PHIMOSIS	CIRCUMCISSION	25	8	1	1	2	3	4	1	NIL
5	MURUGAN	5/Mch	16	12386	PHIMOSIS	CIRCUMCISSION	25	10	1	1	1	2	4	1	NIL
6	BALA	3/Mch	15	12509	RT. INGUINAL HERNIA	RT. HERNIOTOMY	40	9	1	1	3	4	4	0	NIL
7	LAKSHMAN	6/Mch	19	13423	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	8	1	1	1	3	4	1	NAUSEA
8	KARUPPU	4/Mch	8	16089	PHIMOSIS	CIRCUMCISSION	35	11	1	1	2	3	4	1	NIL
9	KARTHIK	5/Mch	19	16651	PHIMOSIS	CIRCUMCISSION	25	10	1	1	1	2	4	1	NIL
10	VISHNU	4/Mch	16	15078	LT.INGUINAL HERNIA	LT. HERNIOTOMY	40	8	1	1	2	3	4	1	NIL
11	MURTHY	2/Mch	10	16073	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	11	1	1	1	2	3	1	NIL
12	BABU	6/Mch	20	16830	PHIMOSIS	CIRCUMCISSION	20	9	1	1	1	2	3	0	NIL
13	KAVERI	6/Fch	18	17961	LT. INGUINAL HERNIA	LT. HERNIOTOMY	35	8	1	1	3	4	4	0	NIL
14	PANDI	2/Fch	10	19053	RT.INGUINAL HERNIA	RT. HERNIOTOMY	40	12	1	1	1	2	4	0	NIL
15	SANTHOSH	4/Mch	16	11621	PHIMOSIS	CIRCUMCISSION	25	10	1	1	2	3	4	0	NIL
16	ILAYARASA	1/Mch	9	20569	PHIMOSIS	CIRCUMCISSION	20	12	1	1	2	3	4	0	NIL
17	RAJA	5/Mch	18	20443	RT. INGUINAL HERNIA	RT. HERNIOTOMY	30	11	1	1	1	2	4	1	NIL
18	VENKATESH	3/Mch	13	22062	PHIMOSIS	CIRCUMCISSION	20	8	1	1	1	2	3	0	PRURITUS
19	NAZAR	6/Mch	20	21214	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	9	1	1	2	3	4	1	NIL
20	ANBARASAN	4/Mch	17	22700	LT. INGUINAL HERNIA	LT. HERNIOTOMY	45	9	1	1	2	3	4	1	NIL
21	RAJESH	2/Mch	11	23903	PHIMOSIS	CIRCUMCISSION	30	10	1	1	1	2	3	1	NIL
22	SRIKANTH	4/Mch	15	22317	PHIMOSIS	CIRCUMCISSION	25	10	1	1	3	4	4	0	NIL
23	SUNDARI	4/Fch	17	20512	RT. INGUINAL HERNIA	RT. HERNIOTOMY	35	12	1	1	2	3	4	1	NIL
24	SARASWATHY	2/Fch	12	23346	LT. INGUINAL HERNIA	LT. HERNIOTOMY	40	11	1	1	1	2	3	1	NIL
25	SHIVA	5/Mch	19	23445	PHIMOSIS	CIRCUMCISSION	25	10	1	1	1	2	3	2	NAUSEA, VOMITING
26	PALPANDI	6/Mch	19	23570	PHIMOSIS	CIRCUMCISSION	20	8	1	1	2	3	4	0	NIL
27	PADMA	1/Fch	8	20452	RT. INGUINAL HERNIA	RT. HERNIOTOMY	45	8	1	1	2	3	4	0	NIL
28	KUMAR	3/Mch	15	20765	PHIMOSIS	CIRCUMCISSION	25	10	1	1	1	2	4	1	NIL
29	LAKSHMAN	2/Mch	12	23476	PHIMOSIS	CIRCUMCISSION	20	11	1	1	2	3	4	1	NIL
30	KIRTHIKA	6/Fch	18	26403	LT. INGUINAL HERNIA	LT. HERNIOTOMY	35	8	1	1	1	2	4	0	NIL

Depart. Anesth

Ref. No. 5336 /E4/3/2012

Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

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1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

21/8/12

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr. Kasirajan. G	M.D Anaesth	Clonidine vs. dexmedetomidine as adjunct to ropivacaine for caudal anesthesia in children.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any
Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8.She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

17.8.12.

DEAN I/c

To
All the above members and Head of the Departments concerned.
All the Applicants.

COMPARATIVE STUDY OF CLONIDINE AND DEXMEDETOMIDINE AS ADJUNCTS TO ROPIVACAINE IN CAUDAL ANALGESIA IN CHILDREN.

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH X (ANAESTHESIOLOGY) APRIL -2013

THE TAMILNADU DR MGR MEDICAL UNIVERSITY

CHENNAI

TAMILNADU